SODIUM THIOSULFATE #94A

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SODIUM THIOSULFATE

A Monograph

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SUMMARY *

Humans appear to be able to tolerate high levels of sodium thiosulfate but use in foods, according to NAS/NRC, is very low. It is also a normal constituent of human and higher animal sulfur pools. The pharmacologic effects that are observed appear to be related to the relatively nonspecific anti-oxidative properties or salt effects and are short-lived due to the rapid metabolism and excretion of this salt.

Toxicity

One of 5 dogs succumbed after an injection of 1.9 gm/kg of anhydrous sodium thiosulfate. The survivors presented metabolic acidosis along with hypoxemia, increased arterial and venous pressure, tachycardia, tachypnea and ECG changes, most of which were probably due to the hyperosmolality and hypernatremia (80). Five humans failed to evoke "symptoms or signs" when they received 64.8 gm (ca 1.08 gm/kg) over a 12 hr period and two other volunteers receiving 200 and 250 gm (3.3 and 4.2 gm/kg) i.v. over a 2 week period failed to disclose any changes of blood morphology or blood chemical findings from those parameters followed (201). However, slight to moderate cyanosis was reported in human patients after 1-2 weeks on a schedule of 3 gm/day orally (295). Anasarca has also been observed in human patients treated with the thiosulfate (113). Multiple sclerosis patients have shown improvement in their condition with no observed side affects after receiving injections of 10-33 mg/kg almost daily for up to 66 days (231).

* References listed in the secondary source material bibliography at the end of this monograph have been searched for pertinent data.

At a level of ca 125 mg/kg daily i.m. rats developed deleterious changes in various organs. Changes in the capillary walls of the thyroid and adrenal cortex were visible at 4 weeks and after 3 months the vessels of the kidneys displayed clear changes, including atrophy of the glomerula and dilation of the glomerular capillaries which were permeable to plasma. An increased permeability of liver capillary walls and an increase in Kupffer cells were noted (306).

Pharmacology

A variety of pharmacologic activities have been reported for thiosulfate. Some of these activities are related to the strong reducing capabilities of the anion and others to chelating properties (S4,294).

The intravenous administration of 0.49 or 0.97 gm sodium thiosulfate caused a remission of allergic diseases in humans, including migraine, urticaria, Arthus reaction and serum anaphylaxis (160). Guinea pigs sensitized to human or bovine serum did not respond with a typical anaphylactic reaction when 2% sodium thiosulfate was added to the provoking serum (153). This anti-allergic response appears to involve a direct action on some protein fraction (153) but may be related, in part, to a rise of histaminase and cholinesterase activity of the guinea pig's blood (146).

Sodium thiosulfate reactivated thyrotrophin (TSH) which had previously been deactivated by treatment with iodine, *in vitro*. Two bioassay procedures were employed; when injected into guinea pigs cuboidal epithelial cell height of the thyroid indicated that 55% of activity was restored (174) and pretreatment with 10^{-1} M thiosulfate restored some mouse TSH activity as measured by the rise of circulating I^{131}, previously injected (347). Large doses (1-2gm) of sodium thiosulfate are able to increase blood and liver levels of glutathione (12) and the concomitant increase in oxygen saturation and oxygen capacity by thiosulfate action on this oxidation catalyst has been clinically useful in the therapy of thromboangiitis obliterans (314). The oxygen saturation of hemoglobin, however, was found to decline in humans from an average of 94.5% before dosing to 88.5% after receiving 3 gm thiosulfate daily orally. The level returned to normal after treatment had been stopped for 1 week (295).

A variety of effects on blood and blood components have also been reported. A three-fold stimulation of the phagocytic activity of polymorphonuclear leukocytes *in vitro* was accomplished by 0.0I N solutions of thiosulfate (191). *In vitro* inhibition of clot formation by 0.017 gm thiosulfate per cc blood was unaffected by the addition of calcium, thus indicating that the chelation of calcium is not significant. Because large doses are required to elicit an inhibitory clotting response in human patients, a probable nonspecific effect is acting. As much as 250 gm were administered over one week in the latter experiment i.v. and this large amount "failed to disclose any changes of blood morphology or blood chemical finding." (201).

Pharmacolytic interaction studies have been noted. A dose of 15 mg/100 ml of a gelatin solution prevented mercurial induced thrombosis in rabbit ears by converting mercuric ions to the mercurous form (264). A 10% thiosulfate solution administered i.v. caused a shift to the right of the LD_{50} (a decrease in the toxicity) of 1-methyl-1-(β-chloroethyl)-ethylimonium picrylsulfonate, a nitrogen mustard, in rabbits (37). The *in vitro* addition of 100-150 mg/kg of thiosulfate blocked the curare activity of D-tubocurarine in the sciatic nerve of the hind leg of the frog (57) while 2g/kg. s.c. antagonized the adrenergic blocking effect of dibenzyline (246).

The oncolytic effects of sodium thiosulfate in the diet or s.c. inhibited the carcinogenic effects of methylcholanthrene and ethylurethane in mice (147) and rats (204) or rabbits (205). Intravenous administration of 33 mg/kg/day did not alter the course of patients with lymphadeno leukemia, Hodgkins disease or lympho sarcoma (262).

Oral fate and metabolism

Thiosulfate is a normal constituent of the urine of higher animals. The output of normal animals on their usual diet has been measured in guinea pigs, rabbits, cows, a horse, cats (S2) and dogs (354, S2). It was not found in the urine of another dog fed 88 mg/kg sodium thiosulfate or other sulfur compounds (289). A few authors have been unable to find low levels of thiosulfate in urine but, presumably, this was due to the insensitivity of earlier methods of analysis (S2). When the 24 hr urine of 28 normal human subjects subsisting on

their usual diets, was assayed by a sensitive and specific procedure thiosulfate was present in all samples, ranging from 2.1 - 16.6 mg (112), and in another study of 8 human subjects on varied diets, sodium thiosulfate output ranged from 5.4 - 8.1 mg/liter (S2).

The level of thiosulfate excreted can be correlated with the protein level of the diet. When human subjects lowered their protein intake thiosulfate output fell correspondingly, and with this fall appeared a concomitant decrease in total sulfur and nitrogen present in the urine (112). Thus, sulfur-containing amino acids are a source of the endogenous thiosulfate pool. This was clearly demonstrated in a study with rats. After an s.c. injection of radioactively labeled S^{35}-cystine 2% of label was found in the urine as thiosulfate. However, when this injection was accompanied by 200 mg of unlabeled sodium thiosulfate pentahydrate to prevent further oxidation of cystine-generated thiosulfate, its fraction of the label jumped to 33% (311). Rat liver extract catalyzed the oxidation of sulfide to thiosulfate (22) and in the presence of rat liver homogenate and sulfite 0.01 M mercaptopyruvate was converted into thiosulfate within 30 min at 37° (303). A sequence of previously established reactions was then formulated through which one molecule of thiosulfate could be produced from two molecules of cysteine with mercaptopyruvate as an intermediate (303).

Orally administered thiosulfate is subject to some attack in the gastro-intestinal tract. At the pH of the stomach it is decomposed *in vitro* into sulfur, sulfite and a few minor products at a rate (S3) competitive with the rate of movement of food through the stomach. In the small intestine some small amount of bacterial metabolism may take place, because the mixed bacterial flora from the comminuted small intestinal mucosa of dogs have been shown to slowly transform thiosulfate into hydrogen sulfide.

More important is the absorption of thiosulfate by the gut mucosa and passage into the portal venous system whereupon it is rapidly excreted or oxidized to sulfate. The previously described artifice which was necessary to prevent the endogenous thiosulfate pool from being converted to sulfate before excretion (311), indicates that oxidation is fairly rapid. Rapid elimination was confirmed when 2 gm of sodium thiosulfate was administered i.v. to normal

CHEMICAL INFORMATION

I. Nomenclature

A. Common names: disodium thiosulfate; "Hypo"; antichlor; sodium hyposulfite; sodium thiosulfate; anhydrous sodium thiosulfate

B. Chemical names: thiosulfuric acid, disodium salt

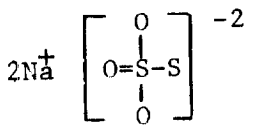
C. Trade name: none

D. CAS Reg. No. 7772987

II. Empirical Formula

$Na_2S_2O_3$

III. Structural Formula



IV. Molecular Weight

158.13

V. Specifications

A. Food Chemicals Codex

assay: 99.0% or more $Na_2S_2O_3$ after drying

water: 32 - 37%

limits of impurities

arsenic (as As): 3 ppm

heavy metals (as Pb): 20 ppm

lead: 10 ppm

selenium: 30 ppm

B. Chemical grade

1. Fisher Chemical Co.

assay (anhydrous powder): 99.5% min

insoluble matter: 0.010%

sulfate and sulfite (as SO_4): 0.30%

sulfide: 0.0001% (1 ppm)

neutrality: passes test

humans and cancer patients; the blood thiosulfate concentration was negligible 45 min post injection and most thiosulfate excreted was collected in 2 hr urine (262). This rapid removal from the blood stream is in part accounted for by distribution into extracellular space (S1). When a human subject received an oral dose of 10 gm, 80% appeared in urine as increased sulfate output by 48 hrs and another 5.5% was thiosulfate within 28 hrs; at 5 gm the same subject passed 5.5% unmetabolized (247); diarrhea occurred at the 10 gm level. A dog of unreported weight excreted 45 and 14% of a 1 gm i.v. and oral dose, respectively, without oxidation (354). In rats, 23 and 85%, respectively, appeared as urine sulfate after oral and i.p. administration (24). From 5-14% of an oral dose appears unmetabolized in the urine, depending on dose and species, but since a significant fraction of an i.v. dose is metabolized to sulfate (24, 311) before excretion this 5-14% represents only a part of the fraction being absorbed into the circulation.

2. MC & B Manufacturing Chemists
   assay (anhydrous powder): 97% min
   heavy metals (as Pb): 0.001% (10 ppm)
   insoluble matter: 0.010%
   sulfide: 0.001% (10 ppm)

VI. Description

A. General: large, colorless crystals or a coarse crystalline powder (Food Chemicals Codex).

B. Physical Properties
   m.p. (pentahydrate) 40 - 45° (loses H_2O)
   b.p. (anhydrous): decomposes at 223°
   sp. gr. (anhydrous): 1.667
   solubility
   500 g/liter in cold water; insoluble in alcohol

C. Stability
   1. fairly stable in air
   2. anhydrous form is deliquescent, pentahydrate effloresces
   3. slowly decomposes in aqueous solution at room temperature

Analytical Methods

1. Spectrophotometric assay in body fluids

Ref. 85

Prepare starch-iodine reagent. Place 20 µl each, of plasma ultrafiltrate, standards and distilled water in separate test tubes. To each add 1.000 ml of starch-iodine reagent, cover, shake, transfer the solution to cuvettes and measure the absorbance at 590 nm.

Alternate procedure: to 200 µl of 2.5% sodium tungstate wash in 50 µl plasma with 200 µl 1/6 N sulfuric acid. Stir and centrifuge. Treat standards similarly except substitute 1.34% sodium sulfate for tungstate and sulfuric acid. Transfer 200 µl standard or unknown centrifugate to test tubes, add 50 µl of water and 1.000 ml of starch-iodine reagent (adjusted with more iodine); measure the absorbance.

Pyruvic acid, ammonium sulfate, sodium arsenite, sodium oleate and glutathione interfere.

2. Spectrophotometric assay in urine

Ref. 112

Adjust urine samples to pH 7.0 - 7.5, combine 5 ml with 5 ml of ethanol and centrifuge. Stir 100 mg of triethylenediamine nickel (II) nitrate with the supernatant, refrigerate overnight and centrifuge. Decant off the liquid, wash the precipitate with 1:1 ethanol:water and recentrifuge. Dissolve the precipitate in a measured volume of KI-dilute sulfuric acid soln and adjust the pH to 1.5 to 2.0 with 9 N sulfuric acid. Add 5 ml of iodine soln, determine the absorbance at 355 nm, quantitating by the method of standard additions. The usual substances found in urine do not interfere with the determination.

3. Titrimetric assay in urine

Ref. 354

Transfer a measured volume of urine into a 250 ml volumetric flask, neutralize it and drip in N/10 iodine to excess to insure complete oxidation of all iodine oxidizable substances. Let the soln stand 1/2 hr, then pour in neutral lead acetate, fill to the mark, shake and filter. Precipitate excess lead in filtrate with K_2SO_4, let it stand for 1 hr and refilter. Mix 200 ml of filtrate

with KI and starch solns and a few drops of H_2SO_4. Put in 1 drop of phenolphthalein indicator and just enough 5% NH_3 to develop a rose color. Reform thiosulfate (stoichiometrically 1/2 of original) with an excess of 10% KCN, let the soln stand and increase the volume by 25 ml with 1:3 sulfuric acid before titrating with I_2. Reforming thiosulfate with KCN insures that other reducing agents will not interfere.

Occurrence

A. Plants: thiosulfate is formed in very small amounts by bacterial action[(a)].

B. Animals: it is present in normal human urine at a concentration of 2-17 mg $S_2O_3^{-2}$/100 ml (112) and in the normal urine of dogs, cats, horses, cows, rats and guinea pigs (S2).

C. Natural sources: 1-3 ppm have been found in certain sulfur-spring waters[(a)].

D. Synthetic: sodium thiosulfate is produced commercially by the reaction of sulfides and SO_2, the reaction of sulfur and sulfite, the oxidation of metal sulfides and hydrosulfides[(a)].

E. Use in food: sodium thiosulfate is added to same alcoholic beverages.

(a) Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., vol. 20, p. 231-234.

BIOLOGICAL DATA

I. Acute toxicity

1. Ref. 80

Animal	Sex & No.	Route	Dose mg/kg	Measurement
Dog	?/5	i.v.	1900	LD_{20}

Sodium thiosulfate pentahydrate (1900 mg anhydrous $Na_2S_2O_3$/kg) was injected in 10 ml of water to anesthetized mongrel dogs weighing 13 to 21 kg. One dog died within minutes of the injection. The remaining 4 dogs developed metabolic acidosis within 2 minutes of drug administration with a slow progressive return to preinjection values over a three hour period. Concomitant with the acidosis was a hypoxemia, hypernatremia, increase in central venous pressure, increase in arterial pulse pressure, tachycardia, tachypnea, ECG change including flattened, inverted T waves and a decrease in QRS voltage.

2. Ref. 81

Method

Species: human with recurring asthma
Sex: male
Age: 28 years old
Duration of Study: 2 months
Vehicle: water
Dose Schedule: 10 ml of 20% solution (2 gm) sodium thiosulfate i.v. and 10 ml of a 10% solution (1 gm) calcium gluconate i.m. twice weekly
Number: 1

Observations

After a two month treatment for chronic eczema immediately after one treatment period the patient complained of intense distress with the sensation of constriction of the chest, suffocation and lack of air. Cyanosis unrelieved by artificial respiration was quickly followed by death.

3. Ref. 201

Animal	Sex/No.	Route	Dose	Measurement
humans	?/5	i.v.	1.08 gm/kg	No effect dose

Five patients received 64.8 gm of sodium thiosulfate over a 12 hr period. The "patients failed to evoke symptoms or signs." Two volunteers took 200 and 250 gm i.v., respectively, over a two week period and biweekly studies over a 4 month period "failed to disclose any changes of blood morphology or blood chemical findings."

II. Short-term studies

1. Ref. 113

Method

Species: Human

Sex: Male

Age: 45 years old

Duration: ?

Vehicle: water

Dose schedule: 1.5, 3.0 then 4.5 gm administered in a total of 6 doses (ca 25, 50 then 4 x 75 mg/kg).

Route: i.v.

Number: 1

Observations

A patient treated for generalized eczema with sodium thiosulfate developed pitting edema of the lower extremities just over the knees. Body weight was increased by 6 kilos and there was no amelioration of the eczema. Withdrawal of thiosulfate resulted in an increase in urine output containing a small unimportant amount of albumin (80 mg/1).

2. Ref. 231

Method

Species: human, all with multiple sclerosis for various times

Sex: both

Age: 13-48 yrs

Duration of study: up to 66 days

Vehicle: water

Dose schedule: day 1, ca 10 mg/kg; day 2, ca 17 mg/kg; day 3, ca 23 mg/kg; day 4, ca 33 mg/kg; day 5, nothing; then ca 33 mg/kg on each of the next 3 days with a break on day 9, which 4 day pattern was continued until up to 50 injections had been received.

Route: injection

Number of patients: 40

Observations made

No side effects from this treatment appeared; two patients only, occasionally complained about irritation from an injection.

Of 24 chronic-progressive cases 10 improved considerably, 6 moderately, 7 slightly and 1 not at all; of 12 relapsing cases 5

improved very substantially, 2 moderately and 5 slightly; of 4 acute cases 3 improved extensively but the other not at all. The shorter the time that a patient had the disease, generally, the better the improvement.

3. Ref. 295

Method

Species: human patients

Sex: ?

Age: ?

Duration of study: 1-2 weeks

Vehicle: water ?

Dose schedule: 3 gm (ca 50 mg/kg) daily of sodium thiosulfate

Route: oral

Number: 9

Observations

Patients presented slight to moderate cyanosis after 1-2 weeks on this schedule. The oxygen saturation of arterial blood was measured by the method of van Slyke. Oxygen saturation of 9 patients averaged 95.4% (94-97%) before treatment, 88.5% (75-95%) after 1-2 wks on this schedule and was back to 95.6% (94-98) after treatment had been stopped for 1 wk.

Saturation with air of blood samples from thiosulfate treated patients did not saturate the hemoglobin as in untreated cases. An O_2 pressure of 1 atm, however, did produce saturation of hemoglobin with oxygen. The authors conclude that the oxygen-hemoglobin equilibrium had been shifted to the right by thiosulfate, *in vivo*.

4. Ref. 306

Male rats received 0.05 g sodium thiosulfate (ca 125 mg/kg) daily, intramuscularly, for 4 weeks or 3 months, after which time the animals were sacrificed and various organs were examined.

Changes in the capillary walls of the thyroid and adrenal cortex were visible at 4 weeks. The vessels were dilated and exhibited a lowered alkaline phosphatase activity.

After 3 months the vessels of the kidneys displayed clear changes. The glomerula were atrophied and hyaline; proximal tubules were expanded and the arteries were in part expanded and in part exhibited endothelial proliferation which caused a narrowing of the lumen. The capillaries

of the glomerula were dilated and permeable to plasma.

In the liver an increase in interstitial fluid accompanying increased permeability of capillary walls and an increase in Kupffer cells were found.

III. Long-term studies

no information found

IV. Special studies

1. Ref. 147

The addition of 0.4% sodium thiosulfate (ca 600 mg/kg/day) to a stock diet fed to 2 month old albino mice of a strain showing 0.5% spontaneous sarcomas at the age of 1 year and 15% spontaneous pulmonary adenomas at the age of six months inhibited two-fold the development of local tumors up to 110 days, induced by either a 0.9 mg subcutaneous injection of methylcholanthrene or by ethylurethane, whether the ethylurethane was administered parenterally at 0.15 mg or in the diet at 0.15% (ca 225 mg/kg) or 0.075%.

No detrimental effect was detected to be due to the thiosulfate diet in any of the treated groups. Food intake and body weight did not vary significantly from that of control mice.

Similar anticarcinogenic effects due to the thiosulfate were obtained after the administration of 0.015% p-dimethylaminoazobenzene in the diet [ca 22.5 mg/kg].

2. Ref. 204 and 205

Thiosulfate inhibited the formation of methylcholanthrene induced tumors. White 120 gm rats received 1.5, 2 or 2.5 mg of methylcholanthrene s.c. once and then 0.01 gm (84 mg/kg) or 0.02 gm (168 mg/kg) of sodium thiosulfate every 3,4 or 6 days for 4 months. Results are presented in the table.

Inhibition of methylcholanthrene induced tumor formation by thiosulfate

Dose	M* only	M + T**
1.5 mg M; 0.02 g T every 3 days	4 tumors/9 rats	1 tumor/6 rats
1.5 mg M; 0.01 g T every 3 days	5/12	2/7
1.5 mg M; 0.02 g T every 3 days	13/13	11/15
2 mg M; 0.02 g T every 4 days	7/9	6/9
2.5 mg M; 0.02 g T every 6 days	10/12	10/15

M* = methylcholanthrene T = thiosulfate

Tumors in the two groups were identical histologically, the thiosulfate treated rats, however, presented fewer fluorescent tumors. Once a tumor appeared thiosulfate had no effect.

It was shown that 0.20 gm $Na_2S_2O_3$ i.v. administered before 5 mg methylcholanthrene i.v., increased the biliary excretion of methylcholanthrene in 5 rabbits 3-fold as compared to control rabbits. It was postulated that the increased biliary excretion reduces the quantity of methylcholanthrene available to the growing tumor.

The authors suggest that the retardation of tumor development might be affected by adrenal stimulation by the thiosulfate. They have found a 19% hypertrophy of the adrenal cortex and a 28% reduction in adrenal ascorbic acid content in rats treated with $S_2O_3^{=}$ as compared to a 12% hypertrophy and a 12% ascorbic acid reduction in the methylcholanthrene only group.

3. Ref. 262

Method

Species: humans with various forms of cancer

Sex: not stated

Age: ?

Duration of study: one or several days

Vehicle: water

Dose schedule: 2 gm (ca 33 mg/kg) once, or daily for several days

Route: i.v.

Number: not stated

Observations made

Fever appeared in patients with lymphadeno leukemia, Hodgkin's disease and lymphosarcoma after 1 injection. After several injections lymphadeno leukemia and Hodgkin's disease patients presented an augmentation of temperature, adenopathies and splenomegaly. Substantial, if not total, resistance to x-ray treatment after a series of injections was noted in cases of Hodgkin's disease, lymphosarcoma and lymphadeno leukemia, but there was little variation in leukocyte count noted. However, cases of myeloid leukemia were not resistant to x-ray treatment after thiosulfate. One acute myeloid "subleukemia" patient, previously in a state of equilibrium with no fever and a

leukocyte count of 10,000 (29% hemocytoblasts), presented angina, elevated temperature, a leukocyte count of 150,000 (90% hemocytoblasts) and ultimately death within 10 days after 6 injections of sodium thiosoufate.

After 1 injection of sodium thiosulfate oxygen consumption increased 4% in hyperthyroid patients, 5% in normal individuals and 8.6% in leukemics. Blood levels of thiosulfate were at their peak 15 min after the injection, being 5.4 mg/100 ml in normal individuals and 4.5 mg/100 in leukemic patients; in all cases, thiosulfate was almost undetectable in the blood after 45 min. Within 2 hrs after injection 4 hyperthyroid patients excreted an average of 21.7% of dose in the urine, 21 normal individuals excreted 18.2% and 11 leukemics excreted 12.7%.

BIOCHEMICAL ASPECTS

I. Breakdown

1. Ref. 322

A 1 ml suspension containing 10 mg of *Thiobacillus X*, physiologically similar to *T. thioparus*, was incubated with 1 μ mole of labeled thiosulfate at 23° and pH 7 in 0.1 M phosphate buffer. Within 10 sec 50% of the thiosulfate had been metabolized; the oxidation to sulfate was complete within 8 min. Tetrathionate was the first intermediate in this oxidation.

2. Ref. S3

Thiosulfate decomposes mainly into sulfur and sulfite in acid solution. After an induction period (time for sulfur to exceed its critical supersaturation concentration) colloidal sulfur begins to appear and can be measured spectrophotometrically. It appears after 2600 sec at pH 3 in 0.00203 M thiosulfate and after 1500 sec at pH 4 and 0.0124 M thiosulfate.

II. Absorption-distribution-metabolism-excretion

1. Ref. 6

Fresh mucosa from the small intestines of dogs were comminuted and 50 gm were combined with 0.002 mole sodium thiosulfate. This mixture was incubated at 38° and neutral pH in a highly aerated system for 48 hrs. The hydrogen sulfide which evolved from thiosulfate was collected and the amount corrected for sulfide coming from the mucosa itself. The intestinal flora in the mucosa converted 18.6% of the thiosulfate to sulfide; l-cystine at the same concentration produced 27.9%.

2. Ref. 22

Rat livers oxidize sulfide to thiosulfate. Fresh extracts of perfused rat livers from young adult 200-300 gm male Wistar rats in M/7.5 phosphate buffer at pH 7.3 were incubated at 37° with 2×10^{-2} M sulfide; the rate of sulfide and oxygen disappearance corresponded with the rate of formation of thiosulfate. Two systems are involved: one stable to boiling water and, at least partially, nonezymatic and the more important heat labile system. Both are affected differently by pH, conc. and temperature changes. Sulfur and sulfite are not substrates and ferritin was found to be part of the sulfide oxidizing system.

3. Ref. 24

Fasting female Wistar rats weighing ca. 260 g received $Na_2S_2O_3 \cdot 5H_2O$ (4.51% concentration) by gavage in a volume equivalent to 5% body weight or by intraperitoneal injection in a volume equivalent to 3% body weight (2.54% concentration). Assay of 4-hour urine found ca 23% of the sulfur load excreted as inorganic sulfate after oral administration and approximately 85% after i.p. injection. These results indicate that detoxification of thiosulfate is principally an oxidative process and that tissue absorption is low.

4. Ref. 35

The 2-hour urinary excretion of $Na_2S_2O_3$ administered i.v. in doses of 0.95, 1.8 or 2.6 gm to non-pregnant and pregnant patients being treated for veneral disease was studied. The experimental period lasted from the 23rd week of pregnancy to the 4th week postpartus. In general, it was found that the excretion of $S_2O_3^{=}$ occurs within

a normal range of 19 to 37%; the percentage excreted being directly dependent on the amount of $S_2O_3^=$ injected. Thiosulfate excretion was found to be depressed below the normal range to levels as low as 5% during the last trimester of pregnancy either for a short time or for a prolonged time without apparent etiology; in the short-time group the depression was not extensive, while in the second group the depression was marked and prolonged, persisting at times up to 12 months postpartus. There was no correlation between $S_2O_3^=$ excretion and renal sufficiency or veneral disease.

5. Ref. 36

Female dogs weighing 5.5 to 17.0 kg received i.v. injections of 0.2, 0.5, 1.0 or 2.0 gm of sodium thiosulfate in 10 ml. Urinary excretion of $S_2O_3^=$ after a 2-hour collection period varied from 31 to 93% at 0.2 gm, 42 to 59% at 0.5 gm, 45 to 74% at 1.0 gm, and 62 to 68% at 2.0 gm.

Individual values of 2-hour $S_2O_3^=$ excretion in 6 normal pregnant bitches given 1 gm $Na_2S_2O_3$ were found to be depressed throughout pregnancy in the order of 40 to 44% with a maximum excretory depression to 32 to 36% occuring 14 to 18 days before delivery.

One dog made nephritic by exposure of one kidney to x-irradiation and excision of the other kidney 22 and 23 days before delivery, respectively, resulted in an immediate depression of $S_2O_3^=$ excretion from 38% before the nephritic state to 27% four days before delivery (19 days after nephrectomy) without a subsequent return to pre-nephritic levels after parturition. One dog with a pre-existing moderate renal insufficiency and low $S_2O_3^=$ excretion, developed the characteristic depressive $S_2O_3^=$ excretory pattern during pregnancy without subsequent return to pre-pregnancy levels.

In general it was found $S_2O_3^=$ excretion was markedly depressed 10 to 17% 1 to 2 days prior to and indicative of impending abortion.

6. Ref. 92

The kidneys of 2 male dogs were perfused in a heart-lung-kidney preparation. Thirty minutes after connection to a circulatory fluid containing about 1200 cc defibrinated blood and 400 cc Locke's solution urinary flow commenced. After a thirty minute control

phase 10 cc of a 0.5N thiosulfate solution (0.4 gm) was added to the perfusate. The thiosulfate excretion in the urine collected every 30 minutes was 55.2 and 49.06% in 2 hours in 148 and 173 cc respectively which is in agreement with values excreted *in vivo*.

7. Ref. 112

A quantitative determination of excretion of endogenous thiosulfate was made. Twenty four hour urine specimens were collected from 28 normal human subjects subsisting on their normal diets. Thiosulfate was precipitated from the urine with triethylenediamine nickel (II) nitrate (specific for thiosulfate) and was quantitated. Details of this procedure are provided in the Analytical chemistry section. Concomitantly, urine nitrogen and total sulfur were assayed. Table III indicates that thiosulfate, in small quantity, is a normal constituent of the human inorganic sulfur pool. Its presence appears to correlate roughly with N and total S excretion.

TABLE III

24 Hour Urinary Thiosulfate, Total Sulfur, and Nitrogen Excretion by Healthy Adults

No. of samples	Sulfur				Total nitrogen	
	S_2O_3		Total			
	Average	Range	Average	Range	Average	Range
	mg.	*mg.*	*mg.*	*mg.*	*gm.*	*gm.*
8	11.5	14.9–9.6	1085	1200–1000	14.35	17.2–10.8
8	9.8	16.6–6.2	937	987– 900	13.3	16.7– 5.7
11	10.3	14.8–5.1	858	898– 805	13.5	16.0– 9.6
9	10.2	13.3–5.7	727	760– 700	12.3	14.6– 9.3
12	7.8	12.3–4.7	641	680– 601	10.9	13.6– 9.2
8	6.5	10.8–2.7	582	599– 560	10.2	14.8– 6.7
7	5.6	7.1–3.2	446	490– 404	9.6	12.0– 7.7
7	5.3	9.0–2.1	302	393– 210	8.8	12.9– 6.4

The correlation of thiosulfate sulfur with total nitrogen and total sulfur, assuming multiple linear regression, was evaluated by the method of analysis of variance (24) and the F value obtained was highly significant.

Seven subjects then reduced their protein intake for three days. Thiosulfate fell with lowered protein intake and lowered total sulfur and nitrogen output, indicating a dependence of thiosulfate level on the amount of dietary protein, illustrated in Table IV.

TABLE IV

Typical Effect of Varied Protein Intake on Thiosulfate Excretion

24 hour urine collections were made before the start of the diet period and 3 days after returning to the usual diet. Diet period collections were started simultaneously with increased or decreased protein intake.

Subject	Diet	Sulfur		Total nitrogen
		S_2O_3	Total	
		mg.	*mg.*	*gm.*
K. D.	Normal	5.2	625	13.6
	Decrease	2.7	560	11.3
	"	2.1	270	8.0
	"	2.9	580	7.3
J. H.	Normal	5.7	720	13.1
	"	7.4	987	11.6
	Increase	9.6	1010	13.6
	"	12.3	1200	14.1
	"	14.8	808	16.0
	Normal	8.0	588	12.2

8. Ref. 208

A gauze pad was applied to the shaved stomach of each of two dogs (3.3 kg/3.2 kg) and drenched with a radioactively labeled sodium thiosulfate soln. After 1 hr the gauze pads were removed and excess thiosulfate wiped off. Urine was collected every day until day 4 when the two were sacrificed and their organs assayed for label.

A total of 0.2/0.25 % of the label was absorbed; 41/47 % appeared in the urine within 24 hrs and another 47/40 % appeared there during the next 3 days (the stool level was estimated to bring the level to 100%). The following levels appeared in the organs at sacrifice, in mg x 10^{-6} of sulfur for an estimated 4/5 x 10^{-3} mg absorbed through the skin: skin, 1.5/3.0; muscle, 1.7/1.3; bone, 1.3/1.0; cartilage, 7/11; liver, 3/7; lungs, 14/11; kidney, 10/12; spleen, 8/12. The relative uptake by these organs paralleled the uptake by sulfate in a previous study, suggesting that thiosulfate is oxidized to sulfate before incorporation.

9. Ref. 235

White Leghorn chicks received an oral dose of $H_2S^{35}O_4$ and liver taurine and bile taurocholate were assayed for label 1-6 hrs after dosing. When the chicks were fed a 0.3% supplement of labeled sodium thiosulfate in the basal diet for several days prior to the sulfuric acid, taurine and taurocholate labels were higher than in those which received only $H_2S^{35}O_4$, indicating some thiosulfate label incorporation.

10. Ref. 247

When the author received 1 gm of sodium thiosulfate (ca 16 mg/kg) as a 10% solution i.v., 35% of the original dose was detected

by iodometry in the urine, unchanged, after 6 hrs. When this dose was taken orally no thiosulfate was found in the urine.

With an oral dose of 10 gm $Na_2S_2O_3$ (ca 170 mg/kg) in 200 ml of water, 6.5 gm (as SO_3) of sulfate above pretreatment levels appeared within 24 hrs in the urine and another 1.6 gm (as SO_3) of sulfate during the next 24 hrs, a total of 80% of dose; within 28 hrs 5.5% (548 mg) appeared as unmetabolized thiosulfate. The subject presented diarrhea at this dose level and stool may account for the remainder of the dose. Later, when 5 gm (ca 80 mg/kg) were given p.o. 5.5% unchanged thiosulfate appeared in the urine.

11. Ref. 289

Dogs (11.4 - 14.5 kg) were kept on a constant ration with low but not minimal protein. They were fed various sulfur-containing compounds, after which administration urine analyses were made.

A 14.5 kg dog received 2 gm $Na_2S_2O_3 \cdot 5H_2O$ (88 mg $Na_2S_2O_3$/kg) on day 1, 66 mg/kg on day 3 and 44 mg/kg on day 5. The authors conclude "that moderate doses are readily oxidized to sulfates" [and it appears that no thiosulfate was found in the urine].

"No appreciable amounts" of thiosulfate were found in the urine following ingestion of up to 7.0 gm cysteic acid, up to 6 gm taurine or up to 8.2 gm isethionic and no thiosulfate was found after a dose of 7.5 gm cystine.

12. Ref. 303

In the presence of 2% liver homogenate and 0.02 M sulfite 89% of 0.01 M mercaptopyruvate was converted to thiosulfate when incubated for 30 min at 37° and pH 7.4. The factor in the homogenate was heat sensitive; kidney and the cell fraction of blood were also active.

The authors state that it is possible to formulate a sequence of established reactions, through which one molecule of thiosulfate can be produced from two molecules of cysteine, with mercaptopyruvate as an intermediate.

13. Ref. 311

Rats were injected subcutaneously with 0.8 mg of S-35 labeled cystine with or without a concomitant injection of 200 mg unlabeled

$Na_2S_2O_3 \cdot 5H_2O$. In those given thiosulfate the dose was repeated at hr 24. Urine was collected at set intervals and analyzed for thiosulfate by the method of ref. 112 in the analytical section, sulfate and residual sulfur. The results from those rats which received only cystine are presented in table 1 and the results of those also receiving thiosulfate are presented in table 2.

Table 1. Activities of Excreted Thiosulphate, Sulphate and Residual Sulphur
Results are expressed as a percentage of total activity of urine, after injection of 0·8 mgm. of cystine-^{35}S (4 animals)

Time (hr.)	Activity of thiosulphate		Activity of sulphate		Activity of residual sulphur	
	Range	Average	Range	Average	Range	Average
0–6	1·79–2·28	2·1	46·5–78·5	71·8	19·3–31·4	26·0
6–24	1·88–3·22	2·47	53·7–77	67·4	20·7–41·5	30·1
24–48	2·45–3·00	2·64	51·2–68·8	62·6	28·1–45·5	34·2
48–72	1·69–2·71	2·36	53·72	60·8	26·4–43·5	36·5

Table 2. Activities of Excreted Thiosulphate, Sulphate and Residual Sulphur
Results are expressed as a percentage of total activity of urine, after injection of 0·8 mgm. cystine-^{35}S and 200 mgm. $Na_2S_2O_3.5H_2O$. The dose of $Na_2S_2O_3.5H_2O$ was repeated after 24 hr. (6 animals)

Time (hr.)	Activity of thiosulphate		Activity of sulphate		Activity of residual sulphur	
	Range	Average	Range	Average	Range	Average
0–6	38·5–53·2	43·6	31·7–51·8	44	12·0–15·0	13·5
6–24	1·9–19·5	7·6	58·7–77·0	65·5	21·2–30·0	25·4
0–24	20–41	33	47–52	49	12–19	18
24–48	10·2–30·9	16·05	30·0–60·4	51	19·7–39·2	28
48–72	2·5–7·3	5·3	42·5–57·7	52	37·0–52·5	42·2

With no additional thiosulfate only a very small percentage of label appeared as thiosulfate, but when large unlabeled doses were given 33% of the sulfur from cystine was excreted as thiosulfate by hr 24. The authors explain that introduction of exogenous thiosulfate inhibits the oxidation of endogenously produced thiosulfate, which indicates that the thiosulfate pool is significant, although oxidized rapidly.

14. Ref. 354

Sodium thiosulfate was administered by different routes and at different dose levels to dogs (weight ?) and 24 hr urine samples were collected and assayed for thiosulfate excretion (see Analytical chem. section). The results are presented in the accompanying table.

Thiosulfate excretion in 2 dogs

	Administration		Excretion			Administration		Excretion	
	mmole		mmole	% of		mmole		mmole	% of
day	$S_2O_3^{-2}$	route	$S_2O_3^{-2}$	dose	day	$S_2O_3^{-2}$	route	$S_2O_3^{-2}$	dose
1	-	-	0.02		9	0.05	i.v.	0.01	0
2	-	-	0.017		10	-	-	0.032	
3	1.0	i.v.	0.465	45	11	2.0	i.v.	1.37	69
4	-	-	0.02		12	-	-	0.036	
5	-	-	0.03						
6	1.0	p.o.	0.175	14	1	2.0	s.c.	0.42	20
7	-	-	0.03		2	-	-	0.04	
8	0.2	i.v.	0.043	7	3	8.0	s.c.	2.30	28

This study also found the following: thiosulfate was present in urine in small amounts, even before dosing; no tetrathionate could be detected in the urine after any administration of thiosulfate; no increase in thiosulfate output was observed after injection of Sufrogel (sulfur).

15. Ref. S2

Thiosulfate in the urine of various species was assayed. Results are presented in the accompanying table. It was concluded that the reason some workers were unable to find thiosulfate in urine was due to the insensitivity of their method.

A cat was fasted for 3 days, 4 guinea pigs for 1 day and a rabbit received a purgative and then put on a partial fast for 2 days and a complete fast for 1 day. The rabbit and cat received physiological saline injections to promote urination. In all species 24 hr excretion increased remarkably above prefast levels (5 x in the cat, 2 x in guinea pigs and 3 x in the rabbit).

After verifying that urinary excretion of thiosulfate was constant 4 rats were given a diet "deprived of sulfur" for 3 days, were fasted for the next three days and then went back to the sulfur free diet for three days more. During fasting they received physiological saline. The 24 hr urinary thiosulfate levels dropped sharply when the animals were fed a sulfur free diet and rose to above preexperiment levels when fasted.

16. Ref. S1

The single injection of thiosulfate (6.7% anhydrous in isotonic saline or 5% dextrose) and the infusion/slope methods for the measurement of extra cellular water was evaluated in 30-50 yr old female patients, not normal but with no discernible cause for disturbance in hydration. The volume of thiosulfate distribution measured by either method did not compare with each other or with the volume of sucrose distribution and not all thiosulfate could be recovered. It was concluded that besides entering extracellular space or being removed by renal clearance some thiosulfate was metabolized, possibly intracellularly.

TABLE I

Content of thiosulfate in the urine of different animals

Species		mg $Na_2S_2O_3$/liter		Diet
guinea pig	[a] group 1	2.93[b]	3.01[b]	bread crumbs, carrots
	[a] group 2	2.44	2.46	rutabegas
rabbit	no. 1	12.60		carrots, potato pealings
	no. 2	9.40		
	no. 3	31.80	30.0	
cow	no. 1	8.1	7.7	dry fodder
	no. 2	7.9		
horse		38.6	54.8	dry fodder, oats
cat	no. 1	64.0	67.0	milk, meat, fish
	no. 2	60.4	52.9	
	no. 3	32.2	34.0	
dog				bread soup, carrots, potatoes
man	no. 1	8.1		varied diet
	no. 2	7.0		
	no. 3	8.9		
	no. 4	7.1		
	no. 5	5.4		
	no. 6	5.8		
	no. 7	5.9		
	no. 8	5.4		

(a) 2 animals/group; (b) results on different days

III. Effects on enzymes and other biochemical parameters

1. Ref. 12

The i.p. administration of 1-2 gm sodium thiosulfate to 390 to 480 gm pigeons for 14 to 30 days causes an increase in glutathione content of the blood from 45 to 62.5 mg/100 ml before treatment to 70 to 84.5 mg/100 ml after treatment and in the liver from 280 to 295 mg/100 gm to 310 to 337.5 mg/100 gm. [The authors do not state that a reduction in body weight (fluid ?) of ca 70 gm was accounted for or could account for a relative increase in glutathione content].

2. Ref. 31

When fresh rat brain particles are incubated in glutamine substrate at pH 7.4 and 30° with 0.13 M thiosulfate and 0.035 M HCO_3^- 16.3 µg NH_3/ml/120 min are formed, while 3.7 µg NH_3/ml/120 min are formed without thiosulfate; other salts are more effective than thiosulfate in inducing NH_3 production.

3. Ref. 39

Sixteen times more streptomycin was necessary to produce bacteriostasis of an *E. Coli* culture when 0.5% sodium thiosulfate was added to the tryptone broth than when no thiosulfate was present. Other reducing agents also had a similar effect on streptomycin.

4. Ref. 104

Oxidation of sulfite with partially purified rat liver oxidase in 0.050 M phosphate buffer at pH 7.8 and 0.005% versene Fe(III) is inhibited 50% in 10^{-3} M sodium thiosulfate.

5. Ref. 191

In vitro studies were made of the effects of $Na_2S_2O_3$ on the phagocytotic activity of polymorphonuclear leukocytes (PMN). A suspension of 2 cc of horse PMN previously washed in 50 ml of a 0.7% NaCl and 1.1% sodium citrate solution per 150 ml whole blood, was added to a test tube to which was also added 0.25 ml of a B. Coli culture in peptone broth and various concentrations of $Na_2S_2O_3$. After 10-20 min samples of the suspension were stained with Loefflers blue stain and 300 PMN cells were counted for phagocytotic activity.

Control values ranged between 20 to 90 bacteria phagocytised per 100 PMN cells while 0.1 N $Na_2S_2O_3$ treated cells ranged from 34 to 70, 0.01 N from 23 to 219, 0.001 N from 42 to 194 and 0.001 N from 53 to 207. The thiosulfate acts as a powerful stimulant at 0.01 N to 0.001 N while a concentration of 0.1 N $Na_2S_2O_3$ can decrease or even suppress PMN phagocytic activity.

6. Ref. 146

The effect of a 2.0 gm i.v. injection of sodium thiosulfate on the histaminase activity of blood was determined. Venous blood was withdrawn from human patients (eczema, gonorrhea, syphillis, tabes) before and 15 min post injection. The blood was defibrinated, combined with 3 µg histamine and 1 ml Tyrode solution, shaken in a special apparatus at 37° for 90 min in an O_2 stream, and finally analyzed for remaining histamine.

Histaminase activity increased 40% after addition of thiosulfate. Cholinesterase activity also increased by 30% (no details provided).

7. Ref. 153

Guinea pigs received a sensitizing dose of 0.1 ml of human or bovine serum i.p. After 14 days shock and death within 10 min were provoked by i.p. injection of 1 ml of the same serum. Lethal shock could be prevented by adding 2% glucose and 2% sodium thiosulfate to the provoking serum or by an i.p. injection of 0.5 ml of 10% sodium thiosulfate prior to injection of the serum. The antianaphylactic effect of the thiosulfate injection lasted for several days with a maximum after 24 hrs. Once the first symptoms of shock were declenched though, no amount of thiosulfate could inhibit the reaction. Also, $Na_2S_2O_3$ added to serum could not prevent sensitization.

If young horses received "a strong dose" of 10% $Na_2S_2O_3$ 4 hrs before bleeding no symptoms were produced when 1 ml was injected into sensitized guinea pigs. Since thiosulfate itself disappears from the blood rapidly thiosulfate is probably operating on some serum fraction.

8. Ref. 160

The administration of $Na_2S_2O_3$ was employed in the treatment of 6 cases of various allergic manifestations including, migraine, urticaria, Arthus reaction and serum anaphylaxis. In general the patients were

treated by the i.v. administration of 0.49 or 0.97 gm $Na_2S_2O_3$ with complete resolution of the disease within minutes.

In one case the $S_2O_3^{=}$ was administered orally at an approximate dose of 2.08 gm daily to a 10 year old female with allergic migraine. Within 2 weeks abdominal pain had ceased and the migraine headaches were greatly reduced. Another case diagnosed as Arthus reaction of the arm responded to 2 separate daily injections of 0.486 gm $Na_2S_2O_3$ each without sequellae.

9. Ref. 174

The inactivation of thyroid stimulating hormone (TSH) by excess iodine and subsequent restoration of activity by sodium thiosulfate was studied in ca 250 g guinea pigs. All animals received an oral pretreatment of 1 ml Lugol soln (containing 250 µg iodine/ml) daily, for 14 days. Then groups of three received, s.c. and daily, either 5 guinea pig equivalents (5 GPE = 0.286 mg) of TSH, 5 GPE inactivated by excess iodine, or 5 GPE inactivated by excess iodine but then treated with N/100 sodium thiosulfate before injection, for three days. On day 4 all animals were sacrificed and their thyroids were examined.

Those receiving TSH exhibited the characteristics of an activated thyroid (average cuboidal epithelial cell height was 15.2 µ compared to 5.9 µ in controls), while the iodine inactivated TSH treated animals presented still quiescent thyroids (7.2 µ average cuboidal epithelial cell height). When the inactivated hormone was further treated with sodium thiosulfate before injection 55% of TSH activity was restored (as measured by cuboidal epthelial cell height of 12.5 µ); further evidence of thyroid stimulation included a loss of colloidal material from the follicles and a high rate of mitosis.

10. Ref. 184

In vitro 10^{-2} M sodium thiosulfate inhibits the amboceptor-complement dependent hemolysis of sheep erythrocytes.

11. Ref. 201

In vitro studies of the effects of varying amounts sodium thiosulfate on clot formation of normal human blood indicated that a concentration of 0.017 gm/cc blood or greater prevented clotting. The

addition of calcium did not induce coagulation of blood rendered incoaguable by the sodium thiosulfate but in the presence of thromboplastin clotting occurred at a normal rapid rate. Addition of the thromboplastin without calcium to the blood will result in clot formation but at a very slow rate, usually 3 to 4 times normal.

Sodium thiosulfate does not disturb the normal clotting mechanism *in vivo* unless rather large amounts of concentrated solutions are employed. A dose of 50 cc of a 50% solution [dose ? Density not given] was required to induce the prolongation of clotting time 2 to 3 fold 1 to 3 days after the injection. The large dose required to initiate this effect suggests a probable nonspecific effect.

12. Ref. 207

Patients presenting paroxysms of malaria received 0.75, 1.5 or 3.0 gm sodium thiosulfate (ca 12.5, 25 or 50 mg/kg) 3 times a day as a 4.5% solution for 5 or 10 days. Of 79 cases 51.3% reacted by cessation of their paroxysms (the proportion at each dose level is not given). In cases which reacted favorably the number of parasites in the blood decreased and the number of eosinophils increased. No harmful effects were observed from this treatment.

13. Ref. 294

Miners suffering from varying degrees of lead poisoning were removed from the exposure area and received 1.95 gm (ca 32 mg/kg) of sodium thiosulfate i.v. in a few ml of water on alternate days. The average ratio of monocytes plus large lymphocytes to small lymphocytes in 18 patients was 1.23, which rose to a statistically significant ratio of 3.22 after an average of 16 days, and clinically "improvement under this method of treatment was definitely more rapid than could be accounted for by mere removal of the subject from the lead hazard."

14. Ref. 314

In the treatment of thrombangiitis obliterans the i.v. administration of 1 to 2 gm $Na_2S_2O_3$ at varying intervals to several patients produced a marked increase in the oxygen capacity (4 to 7 vol%) and oxygen saturation (8 to 24%) of blood. Concomitant with the increased oxygen saturation were associated increased peripheral temperatures, decreased pulse rate and decreased blood pressure with an improvement

of the disease.

The authors found that the $Na_2S_2O_3$ slightly increases the content of the oxidation catalyst glutathione and postulate that this increase is responsible for the amelioration of the disease.

15. Ref. 347

Thyroid stimulating hormone (2 mU of TSH) was incubated for 2 hrs with 1 µg of I_2 in Krebs-Ringer-phosphate at pH 7.4. Some samples then received 10^{-1}, 10^{-2} or 10^{-3} M sodium thiosulfate and were incubated for another hr. Aliquots of the treated TSH were injected i.v. into mice which previously received injections of I^{131}. The thyrotrophic effect was measured by the percent increase in circulating radioactivity 2 hrs after the injection. The addition of 10^{-1} M thiosulfate but not 10^{-2} or 10^{-3} M restored some of the TSH activity removed by iodine pretreatment.

16. Ref. S4

Male 20-27 gm ddN strain mice received 0.1 ml of 0.9% NaCl containing radioactive Sr^{85} s.c. Immediately thereafter they received 16 mg $Na_2S_2O_3$ (600-800 mg/kg) s.c. and then again daily for two days. After 72 hrs the animals were sacrificed and their excrement and femur were analyzed for Sr^{85}. Radioactive Sr content in urine was 30% after thiosulfate treatment and 21% in controls; retention in the skeleton was 27%, 7% less than controls. When thiosulfate treatment was combined with 1 mg/day nonradioactive $SrCl_2$ bone label dropped to 20%.

IV. Drug interactions

1. Ref. 37

Female albino 220-240 gm rats and male albino 2.0-2.5 kg New Zealand rabbits, which fed and drank *ad libitum*, received a 10% aqueous $Na_2S_2O_3 \cdot 5H_2O$ solution i.v. 5-8 min before receiving 1 mg/ml of methyl bis(β-chloro)amine hydrochloride (HN2) in 0.9% NaCl or 1 mg/ml of 1-methyl-1-(β-chloroethyl)-ethylimonium picrylsulfonate (CPS) in 5% dextrose. When doses "such as 1 gm/kg" of thiosulfate pentahydrate were injected prior to HN2 no significant change in the LD_{50} was found, but with this thiosulfate pretreatment the CPS LD_{50} rose significantly. The results are presented in table V.

Table V. *Summary of LD_{50} data on HN2 and CPS in rats and rabbits, with and without TS protection*

	HN2	*HN2 + TS*	*CPS*	*CPS + TS*
Rats*	0.4 to 0.5 mg. Kg. (0.0021 to 0.0026 mM./Kg.)	0.6 mg. Kg. (0.0031 mM./Kg.)	1.8 to 2.0 mg. per kilogram (0.0044 to 0.0049 mM. Kg.)	7.0 to 7.5 mg. Kg. (0.0170 to 0.0183 mM. Kg.)
Rabbits†	2 to 3 mg. Kg. (0.0104 to 0.0156 mM. Kg.)	< 3.0 mg./Kg. < (0.0156 mM./Kg.)	< 2.0 mg. Kg. < (0.0049 mM. Kg.)	8.10 mg. Kg. (0.0195 to 0.0243 mM. Kg.)

*Female rats, Charles River, 220 to 240 grams.
†Male albino New Zealand rabbits, 2.0 to 2.5 kilograms.

In humans suffering from metastatic carcinoma 128 mg of anhydrous thiosulfate/kg, infused i.v. in 5% glucose, helped protect against leukopenia and thrombocytopenia associated with nitrogen mustard treatment, when total doses of 4.8 - 7.6 mg CPS/kg and 2.0 - 4.8 mg HN2/kg were administered in portions over several days. One patient died on this treatment after receiving 2 x 1.6 mg HN2/kg, probabaly from pulmonary embolus. Thiosulfate was more protective of CPS than HN2.

2. Ref. 57

An anticurare action with 100 - 150 mg/kg of $Na_2S_2O_3$ was observed on the sciatic nerve of the hind leg of an anesthetized rabbit previously treated with D-tubocurarine or di(iodoethylate of bis piperidylethyl) piperazine. The absence of a similar action of sodium sulfate indicates the anticurare activity is in the $S_2O_3^{=}$ anion.

The anticurare activity was not related to an anticholinestrase action of the $S_2O_3^{=}$.

3. Ref. 77

Five artifically respired dogs (10.5 - 19 kg) received 20 mg/kg of malonitrile i.v. After an initial rise arterial pressure fell (measured in one dog), CO_2 production (cm^3/min/kg) dropped 13 - 28.5% and O_2 absorption (cm^3/min/kg) fell 47.8 - 81.9% below normal. These parameters remained depressed for extended periods of time. I.v. injection of a 10% solution of sodium thiosulfate (400 mg/kg) brought these values to normal fairly rapidly.

4. Ref. 244

Intramuscular administration of 1g/kg of sodium thiosulfate to adult Swiss W mice 5 min before i.p. injection of malonitrile raised the LD_{50} of malonitrile 8x, from 13 mg/kg without thiosulfate. Increasing the thiosulfate dose to 1.5 gm/kg produced no further change in the malonitrile LD_{50}.

5. Ref. 246

. Male 320 - 380 gm Sprague-Dawley rats received 3.0 mg/kg of dibenzyline i.m., preceded and/or followed by 2.0 g/kg of sodium thiosulfate s.c. initially, and then 1.0 g/kg/hr as a 10% solution in water. This dose maintained a thiosulfate blood level of 100 mg/100 ml, which antagonized the adrenergic blocking of dibenzyline. Heparin was administered, blood pressure was recorded through a cannulated carotid artery and increasing challenge doses of adrenaline·HCl (1.0 to 1000 µg/kg) were injected in the femoral vein to determine the extent of adrenergic blockade.

Dibenzyline produced complete blockade of pressor responses up to 1000 µg/kg adrenaline, the maximum level tested. When thiosulfate treatment was begun 2 hrs before the dibenzyline injection and continued to the challenge dose with adrenaline (up to 12 hrs, the maximum time the animals remained in good condition), this treatment almost completely prevented the development of dibenzyline blockade. Partial reversal was seen in 2 animals at 2.0 µg/kg adrenaline and 1 at 1.0 µg/kg but there was no blockade at all in the 5 others.

In another group thiosulfate treatment was initiated 1 to 18 hrs after dibenzyline injection and continued to the challenge test 2, 5 or 10 hrs later; thiosulfate had little effect here. When it was given 2 hrs prior to dibenzyline and continued for 4 to 10 hrs, which was 5 or 10 hrs before adrenaline challenge when blood levels of thiosulfate were 20 mg/100 ml or less, partial but significant adrenergic blockade was observed in all animals.

6. Ref. 264

The addition of 15 mg/100 ml sodium thiosulfate to a gelatin solution of 4 mg/100 ml phenyl mercuric borate, a mercurial preservative, significantly prevented the mercurial induced thrombosis in rabbit ears after intravenous injection of the solution. The protective effects of the thiosulfate is attributed to its reductive properties converting mercuric ions to the mercurous form rendering the compound less irritative.

Consumer exposure information

Summary of possible daily intake of sodium thiosulfate from NAS/NRC comprehensive GRAS survey, Oct. 1972, table 13A.

Possible daily intake as mg sodium thiosulfate

Food Category	Age	Average[1]	High A[2]	High B[3]
Alcoholic beverages	0-5 mos	0.0[4]	0.0[4]	0.0[4]
	6-11 mos	(5)	0.00001	(5)
	12-23 mos	(5)	0.00002	(5)
	2-65 yrs	0.00325	0.00944	0.01625

(1) Usual additive use and mean consumption

(2) Usual additive use and high consumption

(3) Maximum addtive use and mean consumption

(4) Usage at levels below 0.00000%

(5) Usage levels are either negligible or unknown

Summary of levels of sodium thiosulfate used in regular foods. Data provided by the NAS/NRC comprehensive GRAS survey, Oct.,1972, table 2.

Food Category	No. firms reporting	Usual use Wtd mean ppm	Max. use Wtd mean ppm
Alcoholic Beverages	(1)	0.1	0.5

(1) 3 or fewer firms reported

The October 1972 NAS/NRC survey does not report use of sodium thiosulfate in any other food category than alcoholic beverages. A previous publication (*Chemicals Used in Food Processing*. Publ. 1274, NAS/NRC, 1965) states that it is used as an antioxidant to prevent precut potatoes from browning and as a stabilizer (0.1%) for KI in iodized salt.

BIBLIOGRAPHY

Those references whose numbers are underlined have been cited in the monograph.

1. Albert, A., R. W. Rawson, P. Merrill, B. Lennon, and C. B. Riddell. 1947. Augmentation of thyrotropic potency by goitrogens. Endocrinology 40:303-307.

2. Alessandrini, A. and N. Sette. 1924. Concerning hemolysin formation from hemolyzed sheep erythrocytes and the action of sodium hyposulfite in the hemolysis, *in vitro*. Ber. ges. Physiol. 24:148.

3. Alsop, W. G. 1954. Bleaching and stabilization of fatty-acid esters. U.S. Pat. 2,684,971. July 27, 1954.

4. Amerio, A. and O. Micelli. 1959. Behavior of clearances of some exogenous substances (inulin, sodium thiosulfate, sodium p-aminohippurate) evaluated during the fall in plasma concentration. Minerva med.:3141-3150.

5. Anderson, J. M. 1963. The kinetics of specific *in vivo* antagonism between intraarterially administered methyl-bis[β-chlorethyl]-amine hydrochloride and intravenous sodium thiosulfate. Cancer (Philadelphia) 16:1281-1287.

6. Andrews, J. G. 1938. Reduction of certain sulfur compounds to hydrogen sulfide by the intestinal microorganisms of the dog. J. Biol. Chem. 122:687-692.

7. Andrews, J. C. 1938. Reduction of some sulfur compounds to hydrogen sulfide with intestinal microorganisms of the dog. J. Biol. Chem. 122:687-692.

8. Anon. 1953. The effect of sodium thiosulphate on coliform and *Bacterium coli* counts of non-chlorinated water samples. J. Hyg. 51:572-577.

9. Anon. 1920. The disulfite compounds of pyruvic and glycerine acids. Ber. Dtsch. Chem. Ges. 14(2):325-334 (1920).

10. Ara, F. 1931. Action of some Bi, Pb, Cu and Hg salts on development of typhoid and coli bacilli. Boll. Soc. Ital. Biol. Sperim. 6(5):406-409.

11. Arcos, J. C., G. W. Griffith and R. W. Cunningham. 1960. Fine structure alteration in cell particles during chemical carcinogenesis. 2. Communication. Evidence for its participation in the mechanism of carcinogenesis. J. Biophysic. Biochem. Cytol. 7:49-60.

12. Arnovljevitch, V. 1931. Increase of glutathione of liver and blood after administration of sodium thiosulphate by intestinal route. Compt. rend. Soc. de Biol. 106:681-682.

13. Aruga, J. 1925. Concerning the kidney function test with thiosulfate. Ber. ges Physiol. 35:119 and Japan J. Dermatol. and Urol. 25:987-1023.

14. Arvanitaki, A. and N. Chalazonitis. 1957. Responses of the neuronic soma (of Aplysia) to photoactivation of the pigmented grains in its cytoplasm. J. Physiol. 49:9-12.

15. Auger, D. and A. Fessard. 1932. On the twitching in a neuro-muscular system submitted to abnormal excitations. Compt. Rend. Soc. Biol. 110(6):41-42.

16. Bacq, Z. M. 1962. Local protective action of macromolecules against loss of hair resulting from x-radiation. Arch Intern. Pharmacodyn. 139:85-91.

17. Baethmann, A, U. Steude, S. Horsch, and W. Brendel. 1970. The thiosulphate (^{35}S) Space in the CNS of rats after ventriculo-cisternal perfusion. Pflungers Arch Eur. J. Physiol. 316(1): 51-63.

18. Bahadur, K. and R. C. Sinba. 1958. The role of 8-hydroxyquinoline in the inhibition of enzymatic activity of papain with Fe^{+2}, Cu^{+2} and Mn^{+2}. Indian J. Appl. Chem. 21:111-113.

19. Baronchelli, A., E. Pieragnoli, and S. Tura. 1957. Roentgen irradiation and sulfhydryl groups: protective action of cystamine, sodium hyposulfite and vitamin B_{12} on the hemolymphopoietic organs, the liver, the pancreas and the adrenal glands. Minerva Fisioter. Tor. 2(3):98-103.

20. Baxter, C. F. and R. van Reen. 1958. The oxidation of sulfide to thiosulfate by metal-protein complexes and ferritin. Biochim. Biophysica Acta (Amsterdam) 28:573-578.

21. Baxter, C. F. and R. van Reen. 1958. Some views about sulfide oxidation by rat liver preparations. Biochim. Biophysica Acta (Amsterdam) 28:567-573.

22. Baxter, C. F., R. van Reen, P.-B. Pearson and C. Rosenberg. 1958. Sulfide oxidation in rat tissues. Biochim. Biophys. Acta 27:584-591 (1958).

23. Bertoni, L. J. 1948. Oxidizing and reducing agents in the stabilization of sweet red wines. Rev. Fac. Cienc. Quim. 23:37-44.

24. Bhagat, B. and M. F. Lockett. 1960. Absorption and elimination of metabisulfite and thiosulfate by rats. J. Pharm. and Pharmacol. 12:690-694.

25. Bieter, R. N. 1933. Further studies concerning the action of diuretics upon the aglomerulant kidney. Jour. Pharmacol. and Exp. Therap. 49(2):250-256.

26. Bilich, I. L. and B. S. Berezovskii. 1959. Cholinesterase activity, glutathione content, and cell permeability in gastric ulcer. Kazan. Med. Zhur. (6):46-51.

27. Binda, G., M. Chirico and M. de Matteis. 1956. Variations in sodium thiosulfate and p-aminohippurate clearance in provoked hypoxemia of anesthetized dogs. Folia cardiol. 15:249-255.

28. Biner, L. and J. Michel. 1934. Effects, of sodium thiosulphate in physiologic solution used in perfusion; experimental study. Nutrition 4:53-58.

29. Binet, L. 1935. The biologically reactive fish. Six Conferences on Physiology, Masson and Co., Paus.

30. Binet, L. and A. Arnaudet. 1931. Quantitative variations of reduced glutathione in the liver under diverse experimental conditions. Compt. Rend. Soc. Biol. 108:1117-1118.

31. Blumson, N. L. 1957. Formation of ammonia from glutamine by rat brain slices. Biochem. J. 65:138-143.

32. Bock, G. and H. Goldhammer. 1951. Meat-tenderizing preparations. Australian 141:755.

33. Boling, E. A. and G. M. Wilson. 1953. Metabolism, effect of changes in renal function on apparent volume of distribution of sodium thiosulfate. S. Forum 4:572-578.

34. Bolliger, A. and M. S. S. Erlam. 1933. The excretion of sodium thiosulfate during uncomplicated human pregnancy after its intravenous administration in large amounts. J. Obstet. Cynacol. Brit. Empire 40:289-298.

35. Bolliger, A. and M. S. S. Earlam. 1931. The excretion of intravenously injected sodium thiosulfate during uncomplicated human pregnancy. Med. J. Australia I:427-34.

36. Bolliger, A. 1929. The excretion of intravenously injected sodium thiosulphate during pregnancy: an experimental study in the dog. Med. Jour. Australia 2(23):806-812.

37. Bonadonna, G. and D. A. Karnofsky. 1965. Protection studies with sodium thiosulfate against methylbis-(B-chloroethyl)amine hydrochloride and its ethyleneimonium derivative. Clin. Pharmacol. Therap. 6(1):50-64.

38. Bonadonna, G. and D. G. Miller. 1963. Protective effect of sodium thiosulfate against nitrogen mustards (rats and rabbit.) In: 54th Annual meeting of the American Association for Cancer Research, Inc. Proc. Amer. Assoc. Cancer Res. 4(1):6.

39. Bondi, A., C. C. Dietz and E. H. Spaulding. 1946. Interference with the antibacterial action of streptomycin by reducing agents. Science 103:399-401.

40. Brinkman, R., H. B. Lamberts, and J. Zuideveld. 1961. Immediate and early x-ray reactions with regard to chemoprotection. II. Irradiation and chemoprotection of fresh synovia as a model of mucopolysaccharide depolymerization. Intern. J. Radiation Biol. 3:279-283.

41. Briz De Negroni, C. 1950-3. Fungistatic and fungicidal action *in vitro* of certain fatty acids and sulfur compounds. Rev. Inst. Malbrain 15:56-58.

42. Buech, H., W. Rummel, K. Pfleger, Ch. Eschrich, and N. Texter. 1968. Urinary excretion of free and conjugated sulfate following administration of N-acetyl-p-aminophenol in rats and men. Nauyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 259(3):276-289.

43. Burnett, W. T., M. L. Morse, A. W. Burke and A. Hollaender. 1952. The reduction of x ray sensitivity of *Escherichia coli* with sodium hyposulfite and other inorganic sulfur compounds. J. Bacteriol. 63:591-595.

44. Burnett, W. T., G. E. Stapleton, M. L. Morse, and A. Hollaender. 1951. Reduction of X-ray sensitivity of *Escherichia coli* B/r by sulfhydryl compounds, alcohols, glycols, and sodium hyposulfite. Proc. Soc. Exptl. Biol. and Med. 77(4):636-638.

45. Busse-Grawitz, P. 1940. Thirty different, typical forms of reaction of the connective tissue after injury with thirty different substances. Beitr. Path. Anat. 104:344.

46. Busse-Grawitz, P. 1941. Thirty different, typical forms of reaction of the connective tissue after injury with thirty different substances. Zentr. Gewerbehyg. Unfallwerhiit. 28:26.

47. Buzzo, A. and R. E. Carratala. 1934. Modification of the original treatment of hydrogen cyanide poisoning with sodium thiosulfate. Semana Med. 14:1757-1764.

48. Campanacci, D. and U. Butturini. 1952. Hepatoprotective effect of sodium hyposulfite in alimentary steatosis due to unbalanced diet. Ateneo Parmense 23:898-914.

49. Carere-Comes, O. 1947. Antianemia properties of sulfhydryl compounds and a combination with iron. Sperimentale 98:238-244.

50. Carminati, G. M. 1965. Pharmacological effects which interfere with the development of experimental inflammatory reactions. Arch Intern. Pharmacodyn. 158(2):339-353.

51. Carpenter, A.-M. 1955. Candida. II. Sensitivity test on strains of Candida. Am. J. Clin. Pathol. 25:98.

52. Carpenter, A.-M. 1955. Candida. II. Sensitivity tests on strains of Candida. Antibiotics & Chemotherapy 5:255-262.

53. Catsch, A. H. Melchinger. 1959. Therapeutic possibilities in poisoning with radioactive disintegration products. VI. The effect of the alkaline earth salts on deposition of radiostrontium. Straklentherapie 109:561-572.

54. Cattaneo, G. and B. Bassani. 1946. Carbonic anhydrase in human pulmonary tuberculosis. Ann. Ist. "Carlo Forlanini" 9(1):9.

55. Charles, AM. 1969. Mechanism of thiosulfate oxidation by *"Thiobacillus Intermedius."* Arch. Biochem. 129:124-130.

56. Chetverikov, G. N. 1963. Cardiac action of strophanthin given with carbohydrate metabolism inhibitors. Farmakol. i Toksikol. 26(1):58-63.

57. Cheymol, J., F. Bourillet, and H. Balestrieri. 1954. Anticurariminetic action of certain thiosulfates. Compt. Rend. Soc. Biol. 148:1062-1065.

58. Chirico, M. and A. Zanzola. 1961. Oxidation of sodium thiosulfate during biliary occlusion by ligature of the bile duct and during liver damage by carbon tetrachloride. Osped. Maggiore 49:55-57.

59. Chirico, M. and A. Zanzola. 1960. Oxidation of sodium thiosulfate in hepatopathic states. Osped Magglors 48:366-370.

60. Chirico, M. and T. Bertolotti. 1958. Importance of sodium thiosulfate oxidation in determing its extrarenal clearance. Osped. Maggiore 46:247-250.

61. Chirico, M. and P. Franzini. 1957. Extrarenal clearance with sodium thiosulfate in liver diseases. Riv. Gastroenter. 9(2):63-69.

62. Chirico, M. and G. Binda. 1956. Behavior of extra-renal clearance of sodium thiosulfate in induced hypoxemia. Biol. Lat. 9(3):433-440.

63. Ciaranfi, E. 1947. Action of cysteine and other thio derivatives on respiration of *Escherichia coli*. Boll. Ist. Sieroterap. Milan. 26:59-61.

64. Cier, A., J.-C. Maigrot and C. Nofre. 1964. The effect of mineral anions on the radiation sensitivity in the mouse. C. R. Hebd. Seances Acad. Sci. 259:3656-3658.

65. Cima, E. V. de, A. Martin, R. D. Sananez, and M. A. Vides. 1965. Serum protein fractionation by sodium thiosulfate. II. Electrophoretic and immunochemical control. Rev. Assoc Bioquim. Arg. 30(160):206-211.

66. Coles, H. G. 1964. Ethylenediaminetetraacetic acid and sodium thiosulfate as protective agents for coliform organisms in water samples stored for one day at atmospheric temperature. Proc. Soc. Water Treatment Exam. 13(4):350-363.

67. Coltorti, M. and G. Giusti. 1956. Biochemical properties of the rhodanese system of human erythrocytes. Enzymologia 17(5/6): 256-262.

68. Combes, T. J. C. 1927. Action of sodium cyanide and sodium thiosulfate on the isolated heart of the toad. Compt. Rend. Soc. Biol. 97:1240-1241.

69. Connors, T. A. and L. A. Elson. 1962. Reduction of the toxicity of "radiometric" alkylating agents in rats with thiol pretreatment. Biochem. Pharmacol. 2:1221-1232.

70. Costantini, A. and G. Ballarin. 1934. The action of various salts introduced by the intravenous route on intestinal paristalsis. Boll. Soc. Ital. Biol. Sper. 9:1029-1032.

71. Cresseri, A. and G. Gadolini. 1958. Urine excretion of acidic aminopolysaccharides and the influence of a dose of hyaluronic acid on the clearance of insulin and thiosulfate in the dog. Boll. Soc. Ital. Biol. Sperim. 34:953-956.

72. Daigaku, N., Igaku-Bu and S. Kyoshitsu. 1957. Biochemical investigation of the erythrocytes of dogs which were made anemic with phenylhydrazine and p-chloronitrobenzene. J. Jap. Biochem. Soc. 29:390-401.

73. Dale, W. M., J. V. Davies, and W. J. Meredith. 1949. Further observations on the protection effect in radiation chemistry. Brit. J. Cancer 3:31-41.

74. Dalton, R. G. 1964. Measurement of extracellular fluid volume in cattle with sodium thiosulfate. Brit. Veterinary J. 120(3):117-;24.

75. Dastugue, G., P. Bastide and P. Pasguier. 1959. A comparison of the action of some effectors on aldolase activity of the muscle and of lyophilized yeast. Bull. Soc. Chim. Biol. 41:743-751.

76. Davey, C. B. and G. C. Papvizas. 1962. Growth and sexual reproduction of *Aphanomyces euteiches* as affected by the oxidation state of sulfur. Am. J. Botany 49:400-404.

77. Delaunois, A. and M. Kreula. 1951. Effects of malonitrile and sodium thiosulfate on respiratory exchange. Arch. Internat. Pharmacodyn. 86:223-226.

78. Demain, A. L., J. F. Newkirk, G. E. Davis, and R. E. Harman. 1963. Nonbiological converstion of cephalosporia C to a new antiboitoc by sodium thiosulfate. Appl. Microbiol. 11:58-61.

79. Dennen, D. W. and D. D. Carver. 1969. Sulfatase regulation and antibiotic synthesis in *Cephalosporium acremonium*. Can. J. Microbiol. 15(2):175-181.

80. Dennis, D. L. and W. S. Fletcher. 1966. Toxicity of sodium thiosulfate (NSC-45624), a nitrogen mustard antagonist, in the dog. Cancer Chemotherapy Rept. 50(5):255-257.

81. Derobert, L. and R. Martin. 1951. Toxicity, sudden death during intravenous injection of sodium thiosulfate. Ann. Med. Leg. 31:233-235.

82. Deyrup, I. J. 1964. The influence of SO_4-transporting and metabolizing substances on $^{35}SO_4$-uptake in the kidney. American J. Physiol. 207:84-88.

83. Diacono, H. 1935. Reversibility of metallic protein compounds by action of sodium thiosulphate; serologic behavior of these compounds coming from hemolytic and syphilltic serums. Arch. Inst. Pasteur de Tunis 24:254-267.

84. Diacono, H. 1934. Reversibility of heavy metal protein precipitation with thiosulfate. Serological relations of such complexes from hemolytic and syphilitic serum. Compt. Rend. Hebd. Seances Acad. Sci. 199:1686-1687.

85. Dixon, K. 1962. Spectrophotometric determination of sodium thiosulphate in body fluids by use of an iodine-amylose complex. Clin. Chim Acta 7:453-458.

86. Dolgova, Z. Ya. 1963. The role of disorder in capillary penetrability in the pathogenesis of acute toxic lung edema. Tr. Semipalatinskogo Med. Inst. 3:190-193.

87. Dowden, B. F. and H. J. Bennett. 1965. Toxicity of selected chemicals to certain animals. J. Water Pollution Control Federation 37(9):1308-1316.

88. Drasil, V. and L. Drasilova. 1956. The influence of sodium thiosulfate on the inactivation of pepsin by radiation. Scripta. Med. Fac. Med. Univ. Brunesis Olonucensis 29:93-100.

89. Duvoir, M., L. Derobert, and A. Girves. 1946. Investigations on the prevention of chronic benzene poisoning. Preliminary note. Rec. Trav. Inst. Nation. Hyg. 2(2):537-549.

90. Effersoe, P. 1951. Ratio between inulin and urea clearance in rabbits with increased urine flow following administration of sodium thiosulfate. Acta Physiol. Scand. 22:168-179.

91. Eggleton, M. G. and Y. A. Habib. 1949. Sodium thiosulfate excretion in the cat. J. Physiol. 110:98-109.

92. Elaut, L. 1931. Excretion of sodium thiosulfate by the perfused kidney. J. Urol. 26:241-246.

93. Elliott, S. R., II, and H. W. Scott, Jr. 1948. Effect of p-amino-hippuric acid on sodium thiosulfate determinants in renal clearance studies. Bull. Johns Hopkins Hosp. 83:213-224.

94. Esposito, S. 1959. The urinary elimination of the dextran molecule as index of glomerular permeability. Relation between the clearance of dextran and the clearance of sodium hyposulfite. Arch. Sci. Med. 108:871-875.

95. Estler, C. J., 1965. The alteration of metabolism in the brain by sublethal potassium cyanide poisoning and its influence by cyanide antagonists. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 251:413-432.

96. Faguet, M. 1962. The inhibitory effect of certain chemical compounds on lysis induction and release of phage upon irradiation of lysogenic *Escherichia coli* cultures with ultraviolet rays. Compt. Rend. 255:1810-1812.

97. Faludi, B., I. Fedorcsak, S. Zgyerka, and A. Muhlrad. 1955. Chemical properties and active group of rhodanese and the mechanism of rhodanese action. Acta Physiol. Acad. Sci. Hung. 7:175-178.

98. Fessard, A. 1954. Prototypes of autorhythmicity, provoked by chemical activation in isolated muscles. Anais Acad. Brasil. Cienc. 26: 219-228.

99. Fiala, S. 1941. On the conditions for dry and adhesive growth and the phenomenon of lysis in *Pseudomonas pyocyanea*. Zentralbl. Bakt. I. Abt. Orig. 148:58-60.

100. Fiessinger, N., H. Benard, J. Courtial and L. Derner. 1936. Combustion of ethyl alcohol during perfusion of the liver. Compt. Rend. Soc. Biol. 122:1255-1258.

101. Fischer, M. H. and H. Lowenbach. 1934. The action potential of the central nervous system under the influence of spasm inducers. II. Cardiazol, Caffein and others. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 174:502-516.

102. Fishback, H. R. 1944. The mobilization of iron in hemochromatosis with administration of various chemicals. J. Lab. Clin. Med. 29:742-744.

103. Fort, M. and V. Moravek. 1936. Abnormal crystallization of salts in serum of healthy and cancer patients. Acta Cancerologica 2:51-60.

104. Fridovich, I, W. Farkas and P. Handler. 1959. Sulfite oxidation in the rat liver. Bull. Soc. Chim. biol. 40:1795-1801.

105. Fujil, K. 1934. Effect of bromobenzene on glutathione content of organs in rats fed with thyroid substance and sodium thio-sulphate. Mitt. a. d. Med, Akad. zu Kloto 11:897-909.

106. Fujino, Y. 1937. Effect of sodium thiosulfate on urobilinuria in tuberculous patients. Kekkaku 15:40.

107. Fujino, Y. 1937. Effect of sodium thiosulfate on urochromogen in urine of tuberculous patients. Kekkaku 15:39.

108. Gajatto, S. 1940. Action of subcutaneously injected cysteine hydrochloride on the reduced-glutathione content of the blood and tissues, on body weight, and on the weights of some organs of the rabbit. Boll. Soc. Ital. Biol. Sper. 15:799-800.

109. Gajatto, S. 1939. Variations in the content in reduced glutathione of blood on tissues following the administration of sulfur preparations. I. Statement of question and reason for the research. Experiments with sodium thiosulfate. Arch. Ital. Sci. Farmacol. 8(2):102-129.

110. Gaschott, O. 1925. Contribution to sensitisation physiology of trout sperm. I. The optimal salt concentration. II. The influence on motility of sperm of pH. Ber. Ges. Physiol. 35. 761.

111. Gascon, J. 1928. The action of some double thiosulfates on normal and tuberculositic sheep. Revista Fac. Ciencias Guim., La Plata 5. part I: 41-42.

112. Gast, J. H., K. Arai and F. L. Aldrich. 1952. Quantitative studies on urinary thiosulfate excretion by healthy human subjects. J. Biol. Chem. 196:875-884 (1952).

113. Gate and A. Friedel. 1934. Toxicity, edema of lower extremities during sodium thiosulphate therapy of eczema; case. Bull. Soc. Franc. de Dermat. et Syph. 41:559-560.

114. Gindin, V. P. 1967. The treatment of alcoholism by the intravenous injection of sodium thiosulfate. Zh. Otd. Vyp. Farmakol. Khimioter. Sredstva, Toksikol. 12.54.897. 1968.

115. Giri, K. V., P. Seshagiri Rao, and A. Rahman. 1949. Influence of vitamin C and oxidizing agents on prothrombin. Proc. Indian Acad. Sci. 30B:316-330.

116. Gobgato, F. 1954. Distribution in the organism and excretion kinetics of some substances. Giorn. Acad. Med. Torino 117:17-24.

117. Goldblatt, S. and C. C. Dennie. 1928. Toxicity, study of toxicity and chemical changes in blood; intravenous administration. Am. J. Syph. 12:369-373.

118. Golyshenkov, P. P. 1960. Therapeutic action of sodium thiosulfate in poisoning of animals by phenol and cerolin. Uch. Zap. Mordvsk. Gos. Univ. (13):164-179.

119. Gras, J. 1952. Fractionation curves with sodium thiosulfate of normal and pathological human serum. Rev. Espan. Fisiol. 7:265-279.

120. Grauert, H. 1954. Cause and therapy of eclampsia. Munch. Med. Wochschr. 96:719-721.

121. Gray, R. D., W. H. Jeb, J. H. McCoy, J. Morrison Ritchie, A. J. Kingsley Smith, E. W. Taylor, J. M. Watkinson, and I. Sutherland. 1953. The effect of sodium thiosulfate on the coliform and *Escherichia coli* counts of nonchlorinated water supplies. J. Hyg. 51:572-577.

122. Halmi, N. S, L. T. King, R. R. Widner, A. C. Hass, and R. G. Stuelke. 1958. Renal excretion of radioiodide in rats. Amer. J. Physiol. 193(2):379-385.

123. Halverson, A. W., P. L. Guss and O. E. Olson. 1962. Action of sulfur-containing salts on selenium poisoning in rats. J. Nutrition 77:459-464.

124. Harada, N. and K. Yamana. 1951. Action of nitrogen mustard on deoxyribonucleic acid and the several protective agents. Nagoya J. Med. Sci. 14:206-211.

125. Haupt, G. 1969. Ordinance on the use of SO_2. Industrielle Obst- und Gemuseverwertung 54(21):635-340.

126. Heger, J. 1930. Effects, effect of sodium thiosulphate and its compounds with metallic salts on growth of bacteria. Spisylek. Masaryk, Univ. (a70)8:1-25.

127. Heller, L. 1949. The therapy for generalized soap intoxication. Med. Klin. 44:1340-1343.

128. Hintz, R. and R. J. Zochowski. 1969. Determination of thiosulfate space in insulin-treated diabetics. Pol. Tyg. Lek. 24(13):478-480.

129. Hiraoka, E. 1942. Quantitative determination of vitamin C for injection, which contains stabilizers. Biochem. J. 36:196.

130. Hiroshi, K. 1967. Post-exercise diuresis. V. Effects of adrenaline and asphyxia upon urinary excretion of endogenous creatinine and sodium thiosulfate injected intravenously. Mie Med. J. 17(2):197-206.

131. Ho, S. 1963. Antitumor drugs. V. Certain combinations of antitumor agents. Yao Hsueh Hsueh Pao 10(5):279-285.

132. Hoather, R. C. 1957. The effect of thiosulfate and of phosphate on the bactericidal action of copper and zinc in samples of water. J. Appl. Bacteriol. 20:180-187.

133. Hochwald, A. 1936. Anaphylactic shock and vitamin C. II. Z. Ges. Exp. Med. 98:578-582.

134. Hochwald, A. 1936. The role of reducing substances in "hyperergic" reactions. Klin. Wochschr. 15:894-898.

135. Hoffman, C., T. R. Schweitzer and G. Dalby. 1941. Fungistatic properties of antiseptics and related compounds. Effect of pH. Ind. Eng. Chem. 33:749-751.

136. Holboll, S. A. 1929. Elimination of sodium thiosulphate in patients with normal kidneys. Ztschr. f. Klin. Med. 111:117-127.

137. Holboll, S. A. 1925. The quantitative estimation of sodium thiosulfate in urine with particular reference to the use to this substance as a functional kidney test. Klin. Wochschr. 4:1636-1640.

138. Hollaender, A. 1955. Change in radiation sensitivity by chemicals. Sonderbande zur Strahlentherapie 32:40-41.

139. Hollman, E. C. M. J. and Th. De Jonge. 1948. The use of Grote's reagent in connection with the determination of methylthiouracil. Pharm. Weekblad 83:1-9.

140. Holmes, E. M. 1969. The volume of distribution of sodium thisulphate in sheep. Res. Vet. Sci. 10(1):73-78.

141. Imes, P. V. and C. W. Jobes. 1950. Stabilized iodized salt and process of making same. U.S. Patent 2,506,568. May 9, 1950.

142. Isimaru, S. 1938. Action of sulfur preparations on the increase of sugar and of lactic acid and on the decrease of alkaline reserve in the blood of rabbits poisoned by carbon monoxide. Mitt. Med. Akad. Kyoto 23:447-479.

143. Isotalo, S. and R. A. Alha. 1952. Thallium sulfate poisoning. Two non-lethal poisonings after accidental eating of peas. Ann. Med. Exp. Biol. Fenn. 30:88-95.

144. Ito, T. S. Ota, and K. Koizumi. 1956. Ring cleavage of kynurenine by chicken liver extract. Osaka Daigaku Igaku Zassi 8:71-72.

145. Iuchi, I. 1958. Decomposition of parathion in living organisms. III. Serum parathion-splitting activity and serum alkaline phosphatase. IV. Distribution of parathion-splitting substance in various organs: comparison with cholinesterase and alkaline phosphatase. Bull. Yamaguchi Med. School 6:1-7, 9-14.

146. Jacob, W. and G. Stuttgen. 1949. Histamine metabolism in human blood relative to its regulation. Klin. Wschr. 27:457-459.

147. Jaffe, W. G. 1948. Influence of sodium thiosulfate on experimental tumor induction. Experientia 4:234-236.

148. Jaffe, W. G. 1945. The activation of papain and related plant enzymes with sodium thiosulfate. Arch. Biochem. 8(3):385-393.

149. Jaramillo, J. and V. B. Haarstad. 1969. The pharmacological effects of selectively released hydrogen cyanide. Eur. J. Pharmacol. 8(1):127-145.

150. Johnston, R. L. 1942. Cardiac depression by mercurial diuretics. J. Lab. Clin. Med. 27:303-307.

151. Josephson, A. M., C. M. Shapiro, S. Rosengvaig, and K. Singer. 1958. Experimental production of Heinz bodies in various hemoglobinopathies and the thalassemic syndromes. J. Lab. Clin. Med. 51:736-743.

152. Kabelik, J. 1933. The therapeutic use of sodium thiosulfate. Presse Med. 41:1315-1317.

153. Kabelik, J. 1932. Antianaphylactic action of serum with thiosulfate. Compt. Rend. Soc. Biol. 110:397-400.

154. Kabelik, J. 1928. The therapeutic action of thiosulfate Ztschr. Immunitatsforsch. Exp. Therapie 58:434-448.

155. Karrer, P., W. Graf and J. Schukri. 1945. The influence of sodium thiosulfate on vitamin B_1 and other thiazolium salts. Helvetica Chim. Acta 28(7):1523-1526.

156. Katznelson, H. 1947. Substitution of thiamine by certain amino acids in the nutrition of *Bacillus paraalvei*. J. Biol. Chem. 167:615-616.

157. Kawasaki, C., T. Shimamoto and E. Hiraoka. 1964. Thiamine activity of thiamine propyldisulfide in the growth of *Lactobacillus fermenti* 36. J. Vitaminol. (Kyoto) 10:161-167.

158. Kayser, A. and G. van der Ploeg. 1965. Growth inhibition of staphylococci by sodium thiosulfate. J. Appl. Bacteriol. 28(2): 286-293.

159. Kikuchi, T. 1965. The pathway of sulfide production in a copper-adapted yeast. Plant Cell Physiol. 6(2):195-210.

160. Klein, J. E. 1938. Sodium thiosulfate in the treatment of allergy. Arch. Pediat. 55:197-205.

161. Kleiner, G. K. and R. I. Iofo. 1959. Stimulation of penicillin formation in *Penicillium chrysogenum* strains by sulfur compounds. Antibiotiki 4(4):24-29.

162. Klemperer, E. 1930. Investigation of treatment of fright by sodium thiosulfate. Wien Klin. Wochschr. 43:812.

163. Kohn, R. and B. C. Costopanagiotis. 1933. On the experimental change of digitalis poisoning. III. Communication. Combination with circulating analeptics and strychnine, as well as experiments in decapitated cats. Nauyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 171:151-161.

164. Koide, S. S. and M. T. Torres. 1964. Effect of various sulfates and glycerol in the heat inactivation of 3α-hydroxysteroid dehydrogenase of rat liver. Biochim. Biophys. Acta 89(1):150-152.

165. Koj, A. 1967. Oxidation of thiosulphate in animal tissues. Folia Biol. 15:49-63.

166. Koj, A., J. Frendo, and Z. Janik. 1967. S-labeled thiosulfate oxidation by rat liver mitochondria in the presence of glutathione. Biochem. J. 103:791-795.

167. Kondrat'eva, E. N. and V. E. Uspenskaya. 1961. Formation of vitamin B_{12} by photosynthesizing bacteria. Doklady Akad. Nauk S.S.S.R. 136:718-719.

168. Kondratjewa, Je. N. 1956. The use of organic compounds by purpur bacteria in the presence of light. Mikrobiologiya (Moscow) 25:393-400.

169. Kononenko, V. Ya. 1967. Effects of sodium thiosulfate on catechol amines of the brain and other organs of rats. Gormony Golovnoi Mozg, Tr. Vses. Nauch. Konf. :228-233.

170. Kononenko, V. Ya. 1964. Some problems in the metabolism of the aorta wall under conditions of altered vascular tonus. Patol. Fiziol. Serd.-Sosud. Sistemy, Tbilissi, Sb. 1:523-524.

171. Kononenko, V. 1962. On the effect of sodium thiosulfate on metabolism of adrenal substances in the body of rabbits under normal conditions and in experimental renal hypertension. Probl. Endokr. Gromonoter. 8:20-25.

172. Kononenko, W. Ja. 1962. On the influence of sodium thiosulfate metabolism of adrenal hormones in the normal dog and dogs with experimental hypertonic kidneys. Endokrinol. Hormontherap. 8(2): 20-25.

173. Kopaczewski, W. 1921. The surface tension and the suppression of shock with sodium hyposulfite. Comptes Rendus de l'Acad. des Sciences 173:451-453.

174. Kracht, J. 1952. The reversible inactivation of the thyrotropic hormone. Arch. Exptl. Path. u. Pharmakol. 214(4):433-440.

175. Krylova, N. N. and L. D. Zueva. 1955. Stabilizing blood used for food and industrial purposes. Referat. Zhur. Khim. (6768):

176. Krylova, N. N. and L. D. Zueva. 1953. Stabilizing blood used for food and industrial purposes. Trudy Vsesoyuz. Nauch. Issledovatel. Inst. Myasnoi Prom. (5):139-145.

177. Kuhn, H. A. and A. S. Loewenhart. 1925. Antagonism between sodium thiosulfate and arsenical compounds. J. Pharmacol. Proc. 25:160-161.

178. Kuki, S. 1930. The ratio of elimination of dyes from both the glomeruli and tubules. Mitteil. Med. Ges. Tokyo 44(4):371-419.

179. Kulchar, G. V. and W. M. Meininger. 1936. Sodium thiosulfate in treatment of scabbies. Arch. Dermatol. Syphilol. 34:218-219.

180. Kuroda, N. 1930. A study of the neutralizing action of sodium thiosulfate after salvarsan intoxication. Jap. J. Dermatol. Urol. 30(1):51-85.

181. Kuster, E., and S. T. Williams. 1964. Hydrogen sulfide formation by Streptomycetes and methods for its detection. Appl. Microbiol. 12:46-52.

182. Lamberts, H. B. 1964. Cardiovascular damage by x-irradiation and the possible chemoprotection against this. Intern. Symp. Radioprotect. Drugs, 1st, Milan:235-241.

183. Lamberts, H. B. and P. Alexander. 1964. Postirradiation changes in solutions of hyaluronic acid exposed to x-rays. Biochim. Biophys. Acta 88(3):642-644.

184. Lange, A. 1961. Inhibition of immune hemolysis by antirheumatic drugs. Z. Rheumaforsch. 20:203-208.

185. Langeron, L., M. Paget, Nolf, V., and J. Duriez. 1950. Sodium dithionite test. The modern procedure for functional renal exploration. Ann. Biol. Clin. 8:121-155.

186. Lauson, H. D. and D. D. Thompson. 1958. Effects in dogs of decrease in glomerular filtration rate on cation excretion during intravenous administration of unreabsorbable anions. Am. J. Physiol. 192:198-208.

187. Lawrence, W., M. S. Tayao, D. Raj Mahajan, R. Page, D. G. Miller, and P. Clapp. 1964. Systemic thiosulfate protection during fractionated regional nitrogen mustard therapy. J. Surg. Res. 4(11):483-494.

188. Lebduska, J. and F. Cervinka. 1930. The action of colloidal magnesium hydroxide and of sodium thiosulfate on the white blood cells. Compt. Rend. Soc. Biol. 103:366-368.

189. Lebduska, J. 1928. Diuretic and cholagogic action of sodium thiosulphate. Compt. Rend. Soc. biol. 98:1171-1173.

190. Lebrum, J. 1949. The clearance of sodium thiosulfate at low blood concentrations in man. J. Urol. Med. Chir. (Paris) 55:745-757.

191. Lebduska, J. and F. Cervinka. 1930. The effect of colloidal magnesium hydroxide and of sodium thiosulfate on leucocytes. Compt. Rend. Soc. Biol. 103:366-368.

192. Lehner, E. and F. Urban. 1927. Changes in the sensitiveness of the skin after intravenous injection of definite chemical irritants, and after intravenous blood injection. Krankheits-Forsch. 4:375-380.

193. LeJohn, H. B., L. Van Caeselle, and H. Lees. 1967. Catabolite repression in the faculative chemoautotroph *Thiobacillus novellus*. J. Bacteriol. 94(5):1484-1491.

194. Levaditi, C. 1926. Chemotherapy of syphilis. Lancet 1:215-217.

195. Liang, Yu-I, C.-C. Chu, C.-C. Chih, Y-L. Tsen, and K.-S. Ting. 1956. Study of antibilharzia drugs. II. Effect of five drugs on the toxicity and therapeutic activity of tartar emetic. Acta Physiol. Sinica 20:133-413.

196. Lieberman, I. and P. Ove. 1958. Catalase requirement for mammalian cells in culture. J. Exptl. Med. 108:631-637.

197. Liener, I. E. 1957. Essentiality of the disulfide linkages in trypsin. J. Biol. Chem. 225:1061-1069.

198. Limongi, J. P. and Giesbrecht, A. M. 1963. Influence of 2-carboxy-benzeneseleninic acid on the renal elimination of sodium thiosulfate (in dogs.) Arch. Intern. Pharmacodyn. 143:530-533.

199. Limongi, J. P. and A. M. Giesbrecht. 1960. Influence of sodium thiosulfate on the adrenergic blocking action of o-carboxy-benzeneselenic acid. Arch. Intern. Pharmacodynamie 128:1-5.

200. Lindsay, P. 1961. Study of the shock produced by polysaccharide preparations form *Escherichia coli* in tumor-bearing rats. Experientia 17:416-417.

201. Litwins, J., L. J. Boyd and L. Greenwald. 1943. Effects, action of sodium thiosulfate on blood. Exper. Med. and Surg. 1:252-259.

202. Lo, C-P. and L. J-Y. Chu. 1944. Quantitative study of the color reaction of phosphomolybdic acid. Ind. Eng. Chem., Anal. Ed. 16:637.

203. Loeper, J. and J. Loeper. 1955. Action of sodium thiosulfate on biliary elimination of methylcholanthrene. Compt. Rend. Soc. Biol. 149:74-76.

204. Loeper, J. and J. Loeper. 1955. Effect of sodium hyposulfite on the methylcholanthrene cancer of rats. Semaine Hop. Paris 31:1982-1985.

205. Loeper, J. and J. Loeper. 1954. Action of sodium thiosulfate and mercaptopyruvic acid on development of methylcholanthrene-induced tumors in the rat. Compt. Rend. Soc. Biol. 148:1800-1802.

206. Loeper, M., J. Cottet, J. Vignalou and J. Parrod. 1939. Action of sodium thiosulfate on tyramine hypertension. Compt. Rend. Soc. Biol. 131:1033-1034.

207. Lorant, S. 1946. The nonspecific chemotherapy of malaria. J. Trop. Med. Hyg. 49:63-67.

208. Lotmar, R. 1961. The absorption by skin and the utilization and reelimination of colloidal sulfur and thiosulfate; studies in rabbits with S^{35}. Z. Ges. Exptl. Med 134:233-241.

209. Lyric, R. M. and I. Suzuki. 1970. Enzyme involved in the metabolism of thiosulfate by *Thiobacillus thioparus:* III. Properties of thiosulfate-oxidizing enzyme and proposed pathway of thiosulfate oxidation. Can. J. Biochem. 48(3):355-363.

210. Lyric, R. M. and I. Suzuki. 1970. Enzymes involved in the metabolism of thiosulfate by *Thiobacillus thioparus:* II. Properties of adenosine-5-phosphosulfate reductase. Can. J. Biochem. 48(3): 344-354.

211. Lyric, R. M. and I. Suzuki. 1970. Enzymes involved in the metabolism of thiosulfate by *Thiobacillus thioparus:* I. Survey of enzymes and properties of sulfite: cytochrome c oxidoreductase. Can. J. Biochem. 48(3):334-343.

212. MacDonald, N. S., F. Ezmirlion, P. Spain, and D. E. Rounds. 1953. Agents diminishing skeletal accumulation of lead. Arch. Indust. Hyg. and Occupational Med. 7(3):217-220.

213. McLean, R. A., J. F. Kerwin, and E. J. Fellows. 1957. Reaction rate and oral effectiveness of certain adrenergic blocking compounds. J. Pharmacol. Exptl. Therap. 119:566-571.

214. McNamara, H. and H. L. Barnett. 1954. Renal excretion of electrolytes in premature infants during administration of sodium salts of unreabsorbable anions. J. Clin. Invest. 33:774-779.

215. Maeyer-Cleempoel, S. de, and J. Barbette. 1967. Effect of small concentrations of sodium thiosulfate on the flora of water samples destined for bacteriological analysis. Trib. CEBEDEAU 20(278): 27-32.

216. Maldague, P. and J. F. Duplan. 1965. Protection by sodium thiosulfate against the lethal effect of x-rays in mice. Compt. Rend. Soc. Biol. 159(5):1063-1066.

217. Malkin, S. I. and D. G. Toumacheva. 1935. Treatment of rheumatic heart infections with densitizing intravenous injections of sodium thiosulfate. Rev. Med. 52:390-397.

218. Manzotti, M. and R. Margaira. 1952. Mode of disappearance from the blood of exogenous substances introduced into the circulation. I. Diffusion. Boll. Soc. Ital. Biol. Sper. 28:917-920.

219. Martignoni, F. and S. Drovanti. 1952. Changes in kidney function caused by administration of sodium thiosulfate. Arch. Sci. Med. 93:152-160.

220. Martin, A., R. D. Sananez, and M. A. Vides. 1965. Serum protein fractionation by sodium thiosulfate. I. Normal values and their relation with values obtained by paper electrophoresis. Rev. Asoc. Bioquim. Arg. 30(160):201-205.

221. Matinyan, G. V. 1968. Effect of chloroprene and thiosulfate on argininosuccinic synthetase, argininosuccinase, and arginase activity. Biol. Zh. Arm. 21(10):16-23.

222. Matsuyama, A. 1956. Studies on microbial growth. XI. Effects of cysteine on the growth of *Escherichia coli*. Nippon Nogei-Kagaku Kaishi 30:149-158.

223. Matsuyama, A. 1956. Investigation of microbial growth. II. Action of cystein on the growth of *Escherichia coli*. J. Agric. Chem. Soc. Japan 30:149-153.

224. Matveev, M. P., I. Veltischiev, A. K. Mashkeev, and A. I. Morozov. 1962. On examination of glomerular filtration in children by means of sodium thiosulfate and endogenous creatinine. Peditar-ria 40:31-36.

225. Meier, L. 1939. Determination of the reduction-oxidation potential of blood (in vitro) and the effect on the potential of the addition of so-called reduction-oxidation substances. Biochem. Z. 303:32-9.

226. Menghetti, E. 1930. Sodium thiosulfate as an antidote. II. New investigation on the transformation of sodium thiosulfate in the organism. Arch. Intern. Pharmacodynamie 39, 74-90.

227. Meneghetti, E. 1929. Liberation of sodium thiosulphate in the body. Boll. D. Soc. Ital. Di Biol. Sper. 4:107-109.

228. Meneghetti, E. 1928. Transformations of sodium thiosulphate in organisms; experiments. Arch. di. Sc. Biol. 12:549-577.

229. Meneghetti, E. 1928. Liberation of sulphur from sodium thiosulphate in body. Boll. d. Soc. Ital. di Biol. Sper. 3:478-481.

230. Merritt, P. P. and C. H. Bailey. 1945. Preliminary studies with the extensograph. Cereal Chem. 22:372-391.

231. Meszaros, K. and L. Laubal. 1936. Treatment of multiple sclerosis with sodium thiosulfate. Fortscher. d. Therap. 12:738-743.

232. Meyer-Bisch, R. and W. Heubner. 1921. The influence of sulfur injections on the articular cartilage. Biochem. Z. 122:128-136.

233. Miller, W. W., M. Delivoria-Papdopoulous, L. Miller, and F. A. Oski. 1970. Oxygen releasing factor in hyperthyroidism. J. Amer. Med. Ass. 211(11):1824-1826.

234. Millo, A. and A. Debenedetti. 1964. Changes in the permeability of the isolated frog heart irradiated with x-rays. Protective action of glucose, of cysteamine, and of sodium thiosulfate. Riv. Biol. Suppl. 2, 151-167, 169-181.

235. Miraglia, R. J. W. G. Martin, D. G. Spaeth, and H. Patrick. 1966. On the synthesis of the taurine from sulfate by the chick. I. Influential dietary factors. Proc. Soc. Exp. Biol. Med. 123(3): 725-730.

236. Miwa, S., S. Tojo, K. Ui, M. Ueno, T. Tsuchiya, S. Yokota, T. Taguchi, H. Mori, S. Kato, T. Kondo, K. Nishihara, and S. Kubonoya. 1963. Clinical studies on meaning of renal clearance values in the diseased kidneys: Interpreting the excessive value of sodium-thiosulfate clearance. In: Proceedings of the 27th annual meeting of the Japanese Circulation Society, part II, Osaka. Japan Circulation Jour. 27(11):820.

237. Mori, A. 1937. The effect of sodium thiosulfate on tuberculin-intracutaneous-reaction. J. Chosen Med. Assoc. 27:24-28.

238. Mori, S., H. Kashida, and A. Kisanuki. 1958. Effect of an oxidizing and a reducing agent on glutamic dehydrogenase. Osaka Daigaku Igaku Zasshi 10:277-280.

239. Y. Mori. 1956. Investigations in nucleic acid systems. 4. Action of oxidizing and reducing agents on the action of ribonuclease. J. Agric. Chem. Soc. Japan 30:54-49.

240. Mudge, G. H., W. O. Berndt, J. Lockhart, and A. Saunders. 1969. Renal tubular secretion-reabsorption of thiosulfate in the dog. Am. J. Physiol. 216(4):843-852.

241. Nagai, M. 1956. Supplemental investigation into the relation between the oxidation of sodium thiosulfate to sulfuric acid and liver function in dogs. Folia Pharmacol. Japan. 52:66-67.

242. Nakamura, T. and R. Sato. 1960. Cysteine-s-sulfonate as intermediate in the microbial synthesis of cysteine. Nature 185:163-164.

243. Nakatsukasa, W. and J. M. Akagi. 1969. Thiosulfate reductase isolated from *Desulfotemaculum nigrificaln*. J. Bacteriol. 98(2): 429-433.

244. Nash, J. G., B. M. Doucet, P. L. Ewing, and G. A. Emerson. 1950. Effects of cyanide antidotes and inanition on acute lethal toxicity of malononitrile in mice. Arch. Internatl. Pharmacodyn. et Ther. 84(2/3):385-392.

245. Nicolas, J., C. Petourand and J. L. Vial. 1933. Toxicity, generalized edema after intravenous injection of sodium thiosulphate. Bull. Soc. Franc. de Dermat. et Syph. 40:362-363.

246. Nickerson, M. 1962. Mechanism of the prolonged adrenergic blockage produced by haloalkylamines. Arch. Intern. Pharmacodyn. 140:237-250.

247. Nyiri, W. 1923. The fate of sodium thiosulfate in the organism. Biochem. Z. 141:160-165.

248. Odava, I. 1963. Strontium extraction from an organism. Genshiryoku Kogyo 11:41-45.

249. Ogawa, E., S. Suzuki, and H. Tsuzuki. 1965. *In vivo* and *in vitro* experiments on elimination of radioactive strontium deposited in bone. Radioisotopes 14(5):422-427.

250. Ogawa, E., S. Suzuki, and R. Fukuda. 1962. Elimination of radioactive strontium. III. Effects of the administration of various salts. Gamma J. Med. Sci. 11:205-213.

251. Okamoto, K. 1955. Experimental pathology of diabetes mellitus. II. Tohoku J. Exptl. Med. 61, suppl. 3:116.

252. Okamoto, K., T. Taii, H. Koso, N. Takenaka, T. Hayakawa and T. Ibaraki. 1955. Investigation into the prevention of experimental Diabetes mellitus with chemical agents. Tohoku J. Exp. Med. 61. Suppl. III:36-61.

253. Okazaki, S. 1955. Investigation into the growth of anaerobic bacteria in media with various reducing agents. Jap. J. Bacteriol. 10:129-133.

254. Ono, T. 1960. Bacterial thiaminase. IV. The influence of S-containing substances on the production of thiaminase by *Clostridium thiaminolyticum*. Vitamin 19(3):357-364.

255. Paget, M., M. Gontier, and J. Liefooghe. 1956. True creatininemia, its determination, normal level, and its variations. Semaine Hop. Pathol. et Biol. 32:1881-1890.

256. Paget, M. and J. Liefooghe. 1953. The causes of possible errors in the determination of (renal) clearance of sodium thiosulfate, and the mixed test: thiosulfate-p-aminohippuric acid. Ann. Biol. Clin. 11:325-326.

257. Paget, M. 1952. The test of renal function with sodium thiosulfate. Documentation Biologste Prat. 6:79-98.

258. Palu, C. D. and A. Ruol. 1954. Determination of glomerular filtration by the clearance of sodium thiosulfate. Arch. Sci. Med. 97:223-247.

259. Panisset, L. and J. Verge. 1922. Action of sodium hyposulfite on the development of microbes. Comptes Rendus sec. de Biologie 86:848-849.

260. Paoletti, C., M. Boiron, R. Trahaut, and J. Berhard. 1957. Protective effect of sodium hyposulfite against tri(3-chloroethyl)amine in rats. Compt. Rend. Soc. Biol. 151(4):643-646.

261. Paolino, W. and F. Gavosto. 1953. Specific effect of administration of sodium thiosulfate or cysteine on the metabolism and clinical picture of patients with tumors. Minerva Med. (Torino) 44:20-31.

262. Paolino, W. and F. P. Gavosto. 1950. Metabolism of sodium thiosulfate in leukemic patients; hyperplastic and anticytostatic action. Le Sang 21:394-400.

263. Pasero, G., A. Bigalli, and A. Zampieri. 1960. Diuresis variation and activity of various diuretics on the excretion of uric acid. Rass. Fisiopatol. Clin. Terap. 32:1345-57.

264. Patek, A. J., F. E. Kendall, J. Victor, A. Lowell, H. Colcher, and D. Seegal. 1946. Venous thrombosis after infusion with gelatin solutions containing mercurial preservatives. Am. J. Med. Sci. 212:561-564.

265. Pirchan, A. and E. Kodieck. 1934. Metabolism of sulphur and its urinary elimination after administration of thiosulphate. Casop. Lek. Cesk. 73:881-886.

266. Quastel, J. H. 1933. Glutathione, iodoacetic acid and glucose metabolism. Nature 131:206.

267. Raingeard. 1935. Sodium hyposulfite in the treatment of ocular troubles due to trypanocides. Trop. Disease Bull. 32:19-20.

268. Rajka, E., S. Krossy, and M. Gozony. 1956. The phathogenesis of urticarialpruritus. III. Quantitative evaluation of the effects of various drugs on morphine-induced pruritus. Dermatologica 112:81-107.

269. Rauss, K., S. Voros and T. Kontrohr. 1964. New observations concerning the production of hydrogen sulfide by intestinal bacteria. Acta. Microbiol Acad. Sci. Hung. 11:35-41.

270. Razorenova, V. A. 1960. The use of some antihemorrhageic preparations in experimental acute radiation sickness. Voprosy Patogeneza, Eksptl. Terapii i Profilaktiki Luchevoi Bokezni :191-203.

271. Reid, C. S. W. and A. T. Johns. 1957. Bloat in cattle on red clover. III. Treatment and prevention with anti-foaming agents. New Zealand Jour. Sci. and Technol. Ser. A. 38(9): 908-927.

272. Rice, C. E., A. A. Drake and J. E. Smith. 1934. Intravenous injection of copper sulfate in combination with sodium thiosulfate in trachoma treatment. Chemiker Ztg. 58:409-411.

273. Riley, H. P. 1957. Chemical protection against X-ray damage to chromosomes. Genetics 42(5):593-600.

274. Ritter. 1949. Recovery from cyanide poisoning. J. Am. Med. Assoc. 140:541.

275. Roques, E., F. Caujolle and J. Rey. 1938. The permeability of the skin for sodium thiosulfate, hydrogen sulfide and sodium sulfides. Bull. Acad. Med. 119:515-518.

276. Rose, C. L., K. K. Chen and P. N. Harris. 1964. Mercury cyanide poisoning and its treatment in dogs. Proc. Soc. Exp. Biol. Med. 116:371-373.

277. Rosenthaler, L. 1943. Influence of rancidity on thiosulfate. Pharm. Acta Helv. 18:271.

278. Roux, A. 1948. Identification of sulfonamides by means of a nitroprusside reagent. Other reactions given by this reagent. Chimie & Industrie 59:61.

279. Roux, A. 1947. Identification of sulfonamides by means of a nitroprusside reagent. Other color reactions given by this reagent. Lyon Pharm. :82-87.

280. Ryoji, S. 1926. Concerning the clinical utility of thiosulfate as a kidney function test. Ber. Ges. Physiol. 35:694.

281. Sakaguchi, T., H. Nishimura, K. Masuda, I. Tsuge, K. Onishi, and H. Tatsumi. 1966. The relation between chemical structure and protective effect of dithiocarbamate derivative against experimental hepatic injury induced by carbon tetrachloride administration in rats. Bioche. Pharmacol. 15(6):756-758.

282. Sakurai, K. Concerning the reformation of methemoglobin. Research *in vitro*. Arch f. Exp. Pathol. u. Pharmak. 107: 287-315.

283. Sasaki, H. 1957. Certain drugs (thio and thiol derivatives in particular) with action against *Candida albicans*. Igaku Kenkyu 27:2679-2692.

284. Sasaki, T. 1957. Biochemical and genetic studies on nucleic acids extracted from streptomycin-resistant avian tubercule bacilli. I. Kekkaky 32:505-508.

285. Satpaeva, Kh. K. 1947. Action of sodium thiosulfate on isolated heart activity. Vestnik. Akad. Nauk Kazakh. S.S.R. 4(4)(25), 48-51.

286. Scanu, A. 1953. Fractionation curves with sodium thiosulfate of the proteins of normal antidiphtheric, and antitetanic horse serums. Rev. Expan. Fisiol. 9:25-30.

287. Scanu, A. 1953. The fractionation curve for serum proteins with sodium thiosulfate. I. Normal human serums. Riv. Ist. Sieroterap. Ital. 28:539-549.

288. Schmid, A. 1969. The effect of mercaptans on the volume and osmolarity of the urine of rabbits. Naunym-Schmiedebergs Arch Pharmakol 264(2):165-171.

289. Schmidt, C. L. A. and G. W. Clark. 1922. The fate of certain sulfur compounds when fed to the dog. J. Biol. Chem. 53:193-207.

290. Schoberl, A., J. Stroder, and L. Heim. 1950. Effect of thiols on erythrocyte permeability. Z. Ges. Exptl. Med. 116:166-178.

291. Segal, B. M. and G. M. Khanlaryan. 1957. Experimental treatment of alcoholism by intravenous injection of sodium thiosulfate. Zhur. Neuropatol. i. Psikhiatrii im. S.S. Korsakova 57:1242-1247.

292. Senda, K. 1960. Irritability of skeletal muscle. Nippon Seirigaku Zasshi 22(5):345-365.

293. Shiba, T. 1955. The influence of sulfur-containing substances on the production of the immune body. I. Effects of sulfhydryl compounds. Nippon Saikingaky Zasshi 10:1035-1041.

294. Shiels, D. O. 1952. The treatment of lead poisoning by intravenous administration of sodium thiosulfate. Med. J. Australia 39:879-882.

295. Shigiya, R. and Y. Ozawa. 1956. Influence of internally used sodium thiosulfate upon the oxygen equilibrium of hemoglobin. Tohoku J. Exptl. Med. 63:383-388.

296. Shimi, I. R. 1959. Factors which influence the free acidity of *Penicillium sponulosum* in a top culture. J. Sci. Food Agric. 10:244-248.

297. Shimomura, O, F. H. Johnson and Y. Saiga. 1963. Partial purification and properties of a luminescence system from Odontosyllis. J. Cellular Comparat. Physiol. 61:275-292.

298. Shirai, N. 1963. The sensitivity of the pregnant uterine muscle of rats. Bull. Osaka Med. School 9(1):36-61.

299. Sinha, R. C. and K. Bahadur. 1957. Comparative study of the activation of papain by bisulfite and ammonium ions. Proc. Natl. Acad. Sci. India 26A, Pt.1, :53-57.

300. Skelton, G. S. 1962. Effect of various chemicals on papain activation. Enzymologia 24:338-340.

301. Slastenova, E. M. and A. Ya. Shurgyin. 1962. Effectiveness of sodium thiosulfate in connection with a deficit of sulfhydryl groups in the blood serum of patients with tuberculosis of the eyes. Sb. Nauchn. Rabot Kirg. Nauchn. Issled. Inst. Tuberkuleza. 2:291-294.

302. Snigiya, R. and Y. Ozawa. 1956. Influence of internally used sodium thiosulfate on oxygen equilibrium of hemoglobin. Tohoku J. Exper. Med. 63:383-388.

303. Sorbo, B. 1957. Enzymic transfer of sulfur from mercaptopyruvate to sulfite or sulfinates. Biochim. Biophys. Acta 24:324-329 (1957).

304. Sorbo, B. H. 1953. Substrate specificity of rhodanese. Acta Chem. Scand. 7:32-37.

305. Steger, C. 1953. Alkaline phosphatase in the thyroid, the adrenal cortex, and in the kidney after treatment with thiouracil and with sodium thiosulfate. Arch. sci. med. 95:272-81.

306. Steger, C. 1953. Sodium thiosulfate, a vascular toxin. Schweiz. Zeitscher. allg. Path. u. Bakt. 16(2):190-196.

307. Steshov, G. I. and A. A. Golovteeva. 1965. Effects on the properties of collagen of the salt used in the alkali salt treatment. Izv. Vysshikh Uchebn. Zavedenii, Tekhnol. Legkoi Prom. (2):75-80.

308. Suh, B. 1969. Formation of thiosulfate from sulfate by *Desulfovibro vulgaris*. J. Bact. 99:210-215.

309. Sumiki, Y., S. Tamura, and K. Satake. 1951. Inhilation and the the autoxidation of oils and fats. I. The influences of sulfur-containing compounds on the autoxidation of methyl oleate. J. Agr. Chem. Soc. Japan 25:237-240.

310. Suzuki, S. 1962. Application of the iodine-azide reaction to microanalysis. II. Influence of pH on the iodine-azide reaction of thiorea and its derivatives. Bunseki Kagaku 11:299-306.

311. Szczepkowski, T. W., B. Skarzynski, and M. Weber. 1961. The metabolic state of thiosulfate. Nature 189:1007-1008.

312. Tanaka, S., I. Kato, Tsuneo Iwamura, and T. Scrimachi. 1953. The buffer ability of sake. I. J. Soc. Brewing 48:24-26.

313. Terada, H. 1961. Effect of thioctic acid on SH groups in blood and liver. Naika No Tyoiki 9:1-6.

314. Theis, F. V. and M. R. Freeland. 1940. Thromboangitis obliterans. Treatment with sodium tetrathionate and sodium thiosulfate. Arch. Surg. 40:190-207.

315. Timm, F. and M. Arnold. 1959. Histochemical investigations on the fate of mercury diuretics and their cysteine derivatives in the rat kidney. Arch. Exptl. Pathol. Pharmakol. 235:478-489.

316. Tokio, K. 1959. Investigation of carcinostatic substances. 21. Action of mercaptocompounds on experimental leukopenia in rats, induced by nitric oxide. Chem. Pharmac. Bull (Tokyo) 7:867-872.

317. Trapi, G. 1929. The dispersion of colloids of the blood plasma during pregnancy and its correction with sodium thiosulfate. Arch. Gynakol. 136:460-477.

318. Treger, J. 1929. Practical experience with sodium thiosulphate. Ceska Dermatol. 10(3):74-80.

319. Tritz, G. J. and J. E. Ogg. 1967. Physical and Chemical conditions inducing the coccoid form of *Vibrio fetus*. Amer. J. Vet. Res. 28(122):123-129.

320. Trudinger, P. A. 1965. The permeability of *Thiobacillus neapolitanus* to thiosulfate. Austral. J. Biol. Sci. 18:563-568.

321. Trudinger, P. A. 1964. Thiosulfate oxidation and cytochrome in *Thiobacillus* X. I. The fractionation of bacterial extract and the properties of cytochrome. Biochem. J. 78:673-680.

322. Trudinger, P. A. 1959. The primary product of thiosulfate oxidation by *Thiobacillus X*. Biochim. Biophysica Acta (Amsterdam) 31:270-272.

323. Tsukamoto, C. and T. Taniguchi. 1958. Comparison of inhibitory effect of various chemical agents of tyrosinase activity by manometric method. J. Invest. Dermatol. 30:305-310.

324. Uranow, J. W. 1955. The distribution of bromine in the nervous system in various functional conditions. Bull. Exp. Biol. Med. (Moscow) 40(7):44-46.

325. Ussanowa, M. I., and Ss. E. Schnol. 1955. The distribution of marked caffein in animals and its passage from mother to offspring. Bull. Exp. Biol. Med. (Moscow) 40(7):41-44.

326. Vandestrate, M. 1933. Action of manganese chloride and of sodium thiosulfate on intoxication by tuberculin and on the sensitivity of the skin to tuberculin in the case of the tubercular guinea pigs. Compt. Rend. Soc. Biol. 112:357-359.

327. Van Reen, R. and M. A. Williams. 1956. Studies on the influence of sulfur compounds on molybdenum toxicity in rats. Arch. Biochem. and Biophys. 63(1):1-8.

328. Vignati, J. and V. Skalak. 1936. Action of sodium thiosulfate and gold sodium thiosulfate on anaphylaxis in guinea pigs. Compt. Rend. Soc. Biol. 121:1639-1641.

329. Voegtlin, C. and H. A. Dyer. 1927. Arsphenamine - sodium thiosulfate treatment of syphilis. Publ. Health Reports 42:1045-1052.

330. Volterra, M. 1932. Treatment of true uremia by intravenous injections of sodium thiosulfate. Sperimentale:177-180.

331. von Fellenberg, Th. and S. Krauze. 1932. Identification of preservatives. Proposals for the 4th edition of the Seiss book on foodstuffs. Mitt. Lebensm. Hyg. 23:111-137.

332. Vorburger, C. 1969. Comparative studies among the renal clearance of $Na\text{-}Cr_2Cr^{51}$ ethylenediamine tetraacetate, inulin and sodium thiosulfate in man. Klin. Wochenschr. 47(8):415-420.

333. Vorburger, C. and F. Reubi. 1969. Renal clearances. Comparative studies of sodium thiosulfate and disodium chromium ethylenediaminetetraacetate-^{51}Cr (EDTA- ^{51}Cr) in man. Minn. Med. 52(1):37-39.

334. Vorob'eva, L. I. 1962. Effect of sodium hyposulfite on biosynthesis of vitamin B_{12} by propionic acid bacteria. Dokl. Akad. Nauk SSSR 146:693-695.

335. Weber, M., T. W. Szczepkowski and B. Skarzynski. 1961. The role of thiosulfate in the formation of sulfate in animals. Acta Biochim. Polon. 8:71-82.

336. Weirich, C. L. and R. Pokoruy. 1942. Athlete's foot control. A report on the efficacy of the sodium thiosulfate footbath as a practical control measure. Soap Sanit. Chemicals 18(3): 97, 99, 117.

337. Wendt, H. 1937. The detoxifying and antiallergic actions of sodium thiosulfate. Deut. Med. Wochschr. 63:1832-1835.

338. Wheelock, J. V. and J. A. F. Rook. 1966. The transfer of N-acetyl-4-aminoantipyrine and of thiocyanate from blood to milk. J. Dairy Res. 33(3):309-316.

339. Whittingham, W. F. and J. F. Stauffer. 1956. The protection of spores of *Penicillium chrysogenum* against the action of ultraviolet radiation. Amer. Jour. Bot. 43(1):54-60.

340. Wiemer, P. 1929. Blood vessel action of sulfide solution in the hearts of surviving warm-blooded animals. Arch. Exp. Pathol. Pharmakol. 143:10-28.

341. Woodward, G. J., L. B. Kingery and R. J. Williams. 1935. The fungicidal power of phenol derivatives. II. Strength in the presence of proteins. J. Lab. Clin. Med. 20:950-953.

342. Yamada, I. 1936. Biochemical study of sulfur compounds: The thiosulfate test for kidney function. Sei-i-kai Med. J. 55:4.

343. Yamada, I. 1935. Sulfur compounds. II. The fate of thiosulfate administered parenterally in the animal body. Sci-i-kai Med. J. 55(4):691-733.

344. Yamagata, S., I. Arai, K. Unoura, T. Aratani, K. Miura, and K. Otomo. 1955. Function of the reticuloendothelial system. V. Effect of various hormones and vitamins on the function of the reticuloendothelial system and the liver. Tohoku J. Exptl. Med. 61:113-125.

345. Yamane, T. 1958. Effect of sodium thiosulphate on the destiny of substances engulfed by histiocytes in the subcutaneous connective tissue affected with the experimental glycosuria. Okajimas Fol. Anat. 30(6):421-425.

346. Yamauchi, Y. 1952. Preservative for fresh fruit. Japan Pat. 4979. Nov. 26, 1952.

347. Yamazaki, E., A. Noguchi, S. Sato and D. W. Slingerland. 1962. The influence of tissue sections and oxidants on thyrotropin (TSH). Endocrinology 71:588-592.

348. Yanagisawa, K. 1936. The influence of inorganic reducing substances on experimental tuberculosis. Japan J. Exptl. Med. 14:395-452.

349. Yanane, T. 1958. Electron microscopic observations in the effects of perision N-2,3-dimercaptopropanol and thiosulfate of sodium on the excretion of histiocytes in the subcutaneous connective tissues affected with experimental glycosuria. Okajlmas Fol. Anat. 31(1):79-87.

350. Yano, M. 1958. Nutritional value of Allium plants. XX. Thiamine excretion in urine and stool following oral ingestion of allithiamine. Vitamin 15:606-612.

351. Yasuda, Z. 1951. Relation between the liver and the amounts of inorganic and ethereal sulfurates excreted in urine. Folia Pharmacol. Japan. 47(3/4) Proc. 114-115.

352. Yokota, S. 1959. Investigation into thiaminase I. 3. The properties of purified thiaminase I. Vitamins (Kyoto) 17: 287-292.

353. Zernter, E. 1920. The chemistry of alcoholic fermentation. Ber. 53B:325-334.

354. Zorkendorfer, W. 1935. On the excretion of thiosulfate and its determination in urine. Biochem. Z. 278:191-194.

SUPPLEMENTARY BIBLIOGRAPHY

S1. Chesley, L. C. and A. Lenobel. 1957. An evaluation of the single injection thiosulfate method for the measurement of extracellular water. J. Clin. Invest. 36:327-334.

S2. Fromageot, C. and A. Royer. 1945. The constant presence of thiosulfate in the urine of higher animals and its physiological significance. Enzymologia 11:361-372.

S3. Kerker, M. 1951. The acid decomposition of sodium thiosulfate. J. Chem. Phys. 19:1324-1325.

S4. Ogawa, E., S. Suzuki, S. Fujii, T. Honma and H. Tsuzuki. 1964. Studies on the elimination of radioactive strontium. 4. Effects of the administration of various compounds. Gunma J. Med. Sci. 13(3):214-220.

SECONDARY SOURCE MATERIAL BIBLIOGRAPHY

1. Toxic Substances List, 1972 edition. Hebert E. Christensen, Editor.

2. The Mutagenicity and Teratogenicity of a Selected Number of Food Additives (EMIC/GRAS Literature Review), Environmental Mutagen Information Center, Oak Ridge National Laboratory, U. S. Atomic Energy Commission, February, 1973.

3. Survey of Compounds Which Have Been Tested for Carcinogenic Activity. Prepared for National Cancer Institute, U. S. Dept. of Health, Education, and Welfare by John I. Thompson Co., Rockville, Md. Vols for 1951 and 1968-1969 and Supplements I and II.

4. Agricultural Statistics. 1972 and thru June 1973.

5. U. S. Imports for Consumption and General Imports. U. S. Department of Commerce, Bureau of the Census, FT 246-71.

6. Chemicals Used in Food Processing. Publication 1274, NAS/NRC, 1965.

7. Synthetic Organic Chemicals, U. S. Production and Sales. 1970.

8. Reports of the Joint FAO/WHO Expert Committee on Food Additives. A continuing series under the general title, "Specifications for the Identity and Purity of Food Additives and Their Toxicological Evaluation."